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Patient Reported Outcomes and Clinical Rating Scales for Fatigue and Cognition in Multiple Sclerosis

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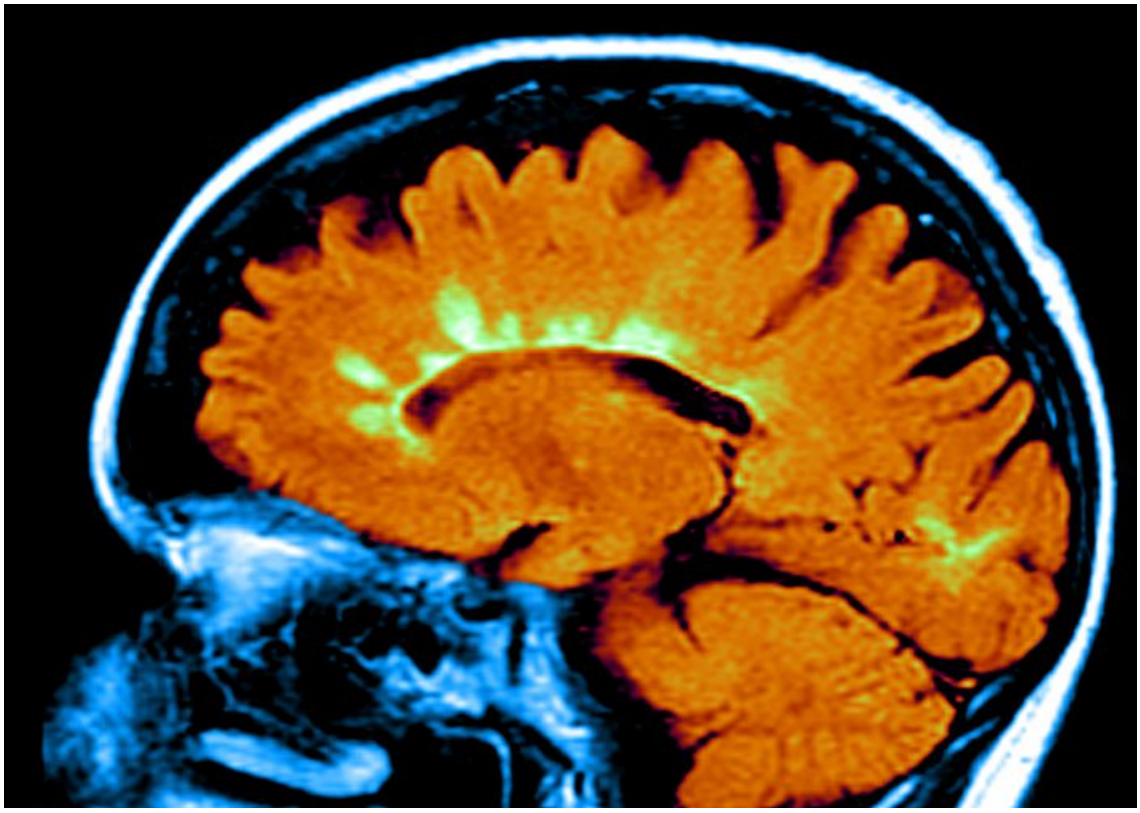
PhD Thesis

Patient Reported Outcomes and Clinical Rating Scales for Fatigue and Cognition in Multiple Sclerosis

Tobias Sejbæk



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Dansk resume

Multipel sklerose (MS) er den hyppigste neurologiske sygdom hos unge voksne. Prævalensen er tredoblet i perioden fra 1950 til 2005, overvejende drevet af en stigning i hyppighed hos unge kvinder. MS er en inflammatorisk sygdom i centralnervesystemet (CNS) som medfører demyeliniserende skade på aksoner og neuroner. Sygdommen kan inddeles i to undertyper: en attakvis og en progressiv fænotype. Begge fænotyper er karakteriseret ved, at patienten over tid udvikler fokale neurologiske symptomer og udviser kognitivt dekline samt kronisk fatigue. Det sidste opleves af mange patienter som det værste symptom ved deres sygdom. Tab af intellektuelle evner, fatigue og aftagende gangfunktion er blandt de hyppigste årsager til pensionering eller reduceret erhvervsevne, hvorfor de udgør en betydelig individuel og socioøkonomisk byrde. Aktuelt tilgængelige behandlinger reducerer attakraten, handicapprogression, og enkelte behandlinger synes at stabilisere patientens kognitive niveau og lindre fatigue. Spørgsmålet om kognitive attakker findes er kontroversielt og har været genstand for intens debat i de senere år. Mange patienter oplever voldsom derudover også fatigue i forbindelse med attak.

Fatigue er det hyppigste symptom hos patienter med MS (65-95%) og opleves hos mere end hver tredje som det sværeste symptom (≈40%). Der findes pt. ikke noget objektivt mål eller en defineret guldstandard til måling af fatigue. Derfor er selvrapportering aktuelt den eneste anvendelige målemetode. Fatigue Scale for Motor and Cognitive Functions (FSMC) er et nyudviklet spørgeskema som er valideret i en tysk MS-kohorte.

Dette ph.d.-studies resultater sammenlignes med valideringsstudiernes data, hvorfor vi anbefaler den danske version af FSMC til klinisk praksis og akademisk brug i Danmark.

MS-patienters kognitive status kan evalueres gennem en standardiseret neuropsykologisk test. Denne proces er dog tidskrævende og bekostelig, hvorfor den ikke er anvendelig i MS-klinikkernes daglige praksis. Der er udviklet testbatterier til screening, som kan udføres af en trænet læge eller sygeplejerske inden for 30 min., hvilket ligeledes begrænser muligheden for implementering af kognitiv screening flere gange årligt. The Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) er et nyudviklet spørgeskema til udfyldning af både patient og nærmeste pårørende med henblik på screening for udvikling af demens. Spørgeskemaet, der er valideret på amerikansk engelsk, argentinsk spansk og hollandsk, er foreslået som et brugbart og omkostningseffektivt screeningsværktøj. Da vi ikke har kunnet demonstrere korrelation imellem resultater af MSNQ og af neuropsykologiske test, konkluderer vi, at MSNQ ikke er brugbar til screening af danske MS-patienter for kognitive problemer. Vores data indikerer at skalaen er påvirkelig af kulturelle og sproglige forskelle samt depressive symptomer hos patienterne. Det kan ikke udelukkes, at positiv publikationsbias forklarer fraværet af negative data om MSNQ.

Symbol Digit Modalities Test (SDMT) er en kort objektiv test udviklet til screening for kognitiv påvirkning af proceshastighed og visuospatial hukommelse. Testen lader sig let implementere i daglig klinisk praksis, da den uden besvær kan udføres af en sundhedsfaglig person på mindre end 5 min. Der savnes undersøgelser af, hvordan resultaterne påvirkes ved gentagen testning, og en læringseffekt ved gentagen testning kan ikke udelukkes.

Nærværende studie viser en signifikant forbedring af SDMT-scoren, når den udføres månedligt i en kohorte af MS-patienter i behandling med natalizumab. Vores gentest af patienter med en anden version af SDMT efter to år demonstrerer, at scoren returnerer til baseline, hvilket formentlig er udtryk for en læringseffekt ved gentagen testning. Vi påviser ligeledes en stabilisering af kognitiv status under og efter 2 års behandling med natalizumab.

English summary

Multiple sclerosis (MS) is the most frequent neurological disease in young adults. Its prevalence has increased by close to threefold from 1950 to 2005, predominantly due to its increasing incidence in younger women. MS is an inflammatory disease of the central nervous system (CNS) that leads to demyelination and axonal/neuronal damage. MS has two major subtypes, a relapsing and a progressive phenotype, both characterized by focal neurological symptoms, cognitive decline, and chronic fatigue. Even without relapses, these symptoms can be severe and disabling. Cognitive decline, fatigue, and walking disabilities are the most frequent reasons for retirement; the individual and socioeconomic consequences are thus substantial. Current treatments can reduce relapse rates and the progression of disability; some appear to stabilize cognitive performance, while a few also have some effect on fatigue. The role of cognitive decline as a sign of relapse or drug failure has recently been intensely debated. MS patients experience fatigue as the most frequent symptom, and often the most severe. Many patients experience severe fatigue along with a relapse or disease progression but also without apparent signs of disease activity.

No objective test has provided a reliable measure of fatigue in MS, and patient-reported outcomes are currently the only way to monitor fatigue. The Fatigue Scale for Motor and Cognitive Functions (FSMC) is a patient-reported questionnaire validated in a German MS cohort. We recently translated the scale into Danish. The results presented in this Thesis are similar to those of the original validation study; we therefore recommend the use of the Danish version of the FSMC in clinical settings and for scientific purposes.

The cognitive performance of MS patients can be measured by a neuropsychological test, but this is time-consuming and hardly feasible in everyday practice. Short cognitive test batteries have been developed for physicians and nurses to screen cognitive impairment in MS. The Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) was created for screening cognitive function in MS patients by their relatives (informants). The questionnaire was successfully developed and validated in American English, and later validated in Argentine Spanish, and has been proposed as a rapid and cost-effective screening tool. However, as the MSNQ scores obtained in our study of Danish MS patients did not correlate with neuropsychological assessment, we conclude that it does not offer a valid and sensitive screening tool for cognitive impairment in Danish MS patients. Our data thus emphasize the importance of validation in different languages, since instruments may be sensitive to cultural and linguistic differences. In addition, the publication of exclusively positive results obtained by validation of new self-reported scales may create a bias, and dependence of self-reported questionnaires on language and culture are going to be missed.

The Symbol Digit Modalities test (SDMT) is a brief, objective screening tool for cognitive impairment that can be administered by a healthcare professional in less than five minutes. The test mainly measures information processing speed and visuospatial memory. SDMT is an ideal rapid screening tool for regular usage due to its easy application. However, a potential learning effect of repeated administration may limit its value. Our examination of monthly SDMT scores in MS patients treated with natalizumab demonstrated significant improvement, with scores increasing when tested monthly.

However, by using a different version of SDMT after two years, the scores returned to baseline. We conclude that frequent application of the SDMT results in a significant learning effect that should be considered. Our study also indicates that cognitive levels, as measured by SDMT, are stable throughout the course of natalizumab treatment.

Abbreviations

ADL: Activities of daily living

BDI: Beck's depression inventory

BDI-FS: Beck's depression inventory fast screen

BICAMS: Brief International Cognitive Assessment for MS

CNS: Central nervous system

CIS: Clinically isolated syndrome

CI: Confidence interval

DMT: Disease-modifying treatment/therapies

EDSS: Expanded Disability Status Scale

FSMC: Fatigue Scale for Motor and Cognitive Functions

MFIS: Modified Fatigue Impact Scale

MS: Multiple sclerosis

MSIS: Multiple Sclerosis Impairment Scale

MSNQ: Multiple Sclerosis Neuropsychological Screening Questionnaire

MSNQ-I: Multiple Sclerosis Neuropsychological Screening Questionnaire reported by informant

MSNQ-P: Multiple Sclerosis Neuropsychological Screening Questionnaire reported by patient

NEDA: No evidence of disease activity

PROs: Patient-reported outcomes

PPMS: Primary Progressive MS

PML: Progressive multifocal leukoencephalopathy

QoL: Quality of life

RRMS: Relapsing-remitting MS

SPMS: Secondary progressive MS

SDMT: Symbol Digit Modalities Test

VCAM: Vascular cell adhesion molecule

Introduction

Multiple sclerosis (MS) is the third most frequent disease of the central nervous system (CNS) after migraine and epilepsy [1, 2]. Northern Europe is a high endemic region, with Denmark having a prevalence of approximately 155/100,000 people (95% confidence interval (CI): 149–160). From 1950 to 2005, the prevalence has increased by a factor close to three, predominantly due to an increase in its incidence in younger women, as the female-to-male ratio increased from 1.31 in 1950 to 2.02 in 2005[3, 4].

MS is a chronic inflammatory demyelinating disease of the CNS that ultimately leads to axonal and neuronal degeneration. Disease onset is usually in early adulthood (age 20–40 years); overall, the lifespan is shortened by five to ten years compared to the background population[4]. Recent studies suggest that the incidence of early death has been reduced as disease-modifying treatments (DMT) have advanced, because earlier diagnosis has contributed to early immunotherapy and the general care of people with MS has improved[5]. DMTs are, however, currently available only for relapsing forms of MS[6]. On average, people with MS live for more than 35 years from time of diagnosis to death[5].

MS phenotypes

According to the traditional classification of MS, 90% present with a relapsing–remitting course (RRMS), and if untreated, 50% of them will move on to a secondary progressive phase (SPMS) fifteen years after the onset of disease[7]. Approximately 10% of multiple sclerosis patients present with primary progressive multiple sclerosis (PPMS).

RRMS is characterized by clinical activity (neurological symptoms and signs), defined as fully or partially recovering relapses, which may be suggested by, for example, blurred vision, paresthesia, paresis, loss of bladder control, or walking disabilities. No or minimal disease progression is seen between relapses (remission). The first relapse is termed clinically isolated syndrome (CIS). Some patients may meet the formal definition of MS with a single clinical episode if their MRI reveals the simultaneous presence of enhancing and non-enhancing lesions. Most patients with RRMS will eventually enter a secondary progressive phase[8, 9].

SPMS begins with a relapsing-remitting course, followed by gradual worsening with or without occasional relapses. Phases with minor remission and disease plateaus are observed. The transition from RRMS to SPMS usually occurs 10 to 20 years after disease onset.

PPMS is characterized by progressive disability. While relapses are rare, plateaus and temporary minor improvements are occasionally seen. Progressive MS subtypes are diagnosed retrospectively, based on patient history and clinical evaluation. A common clinical presentation of PPMS is a spinal cord syndrome with progressive paraparesis, spasticity, and no clear sensory level. Compared with RRMS, PPMS has a more even sex distribution and later onset, usually two decades later in life. The course of PPMS tends to be more aggressive than that of RRMS[4, 10, 11].

A recent update of the MS subtype classification has suggested a two-fold division of the disease into relapsing and progressive forms, each of which has active and inactive stages;[11] this classification may be more appropriate when considering upcoming biological treatments being efficient in progressive MS with inflammatory activity[12, 13].

T-cells and B-cells play an important role in driving CNS inflammation, especially in the early relapsing–remitting disease phases. This is reflected in the treatment response to a monoclonal antibody that prevents lymphocyte trafficking into the CNS: the humanized anti-alpha4-integrin antibody, natalizumab, which blocks the alpha-4 integrin receptor on lymphocytes, inhibits binding to the vascular cell adhesion molecule (VCAM), thereby preventing lymphocytes penetrating the blood–brain barrier[14].

While the evaluation of disease activity, progression, and treatment outcomes has previously focused on relapse rates and patient mobility, attention over the last two decades has moved toward cognition and patient-reported outcomes (PROs). Fatigue, which plays a major role in quality of life (QoL), marital status, and depression, with their attendant socioeconomic impacts, can thus be measured only by PROs[15-17]. Our study focuses on both fatigue and cognition, emphasizing validation and the implementation of clinical testing and patient-reported outcomes in the MS clinic.

Measuring disease activity

Several of the disease-modifying therapies (DMTs) that have been developed over the past twenty years reduce relapse rates and slow the development of disability. Recently, No Evidence of Disease Activity (NEDA)[18] was proposed as a treatment aim.[6] Clinical rating tools, MRI parameters, and possibly self-reported outcomes may be integrated into NEDA outcomes in the future. While criteria have been proposed (NEDA 3 and NEDA 4), no consensus about their application has yet been achieved[19].

Consistent monitoring tools, such as rating scales and self-reported outcomes, are therefore important for clinicians. Most of the currently available PRO scales have been validated only in English or other major languages. It is debated, whether the translated versions reflect the originally intended outcomes. Due to cultural and linguistic differences, validation of translations is essential before their clinical application[20].

The use of scales or questionnaires to measure symptoms raises some important questions—for example, should they be graded dichotomously or with a numeric or analog scale? Could a standardized measurement be achieved by the patient, or a trained clinician is required? Are the scales biased by other symptoms or outcomes? To confirm hypotheses, physicians and neurologists in particular prefer objective measures or paraclinical findings. Some symptoms, such as fatigue[21] and mild cognitive impairment[22] are, however, very difficult to measure by formal testing. Self-reported outcomes could therefore supplement the management strategy in these important domains of MS. Outcomes could also function as screening tools to help target problem areas and facilitate effective communication. PROs can usually be performed in the home, online, or immediately before clinical contact.

Many of the existing PRO instruments have structured scales with different items that enable different perspectives on their domain. Some questionnaires also include different domains, such as overall fatigue, with subscales for cognitive and physical fatigue. Construct validity and reliability are important aspects of the validation of patient-reported outcome scales[20, 23-25].

Fatigue in MS and self-reported outcome measures

Fatigue is a very commonly reported subjective symptom of MS (65–95%). Patients typically describe it as the most severe symptom[26, 27]. Fatigue and mood disorders (depression) have a highly negative impact on QoL[28].

MS patients may experience fatigue as a range varying from the normal tiredness experienced by healthy individuals to more severe and disabling forms that are likely to interfere with personal and social responsibilities.[29] A major challenge in the management of fatigue is the uncertainty over its definition, etiology and pathophysiology, with no gold standard existing among researchers and clinicians.[21] Studies that examine functional brain magnetic resonance imaging and neurophysiology have not been able to clearly distinguish between motor and cognitive fatigue, and rarely differentiate fatigue from fatigability. It also remains unclear whether systemic and central inflammation drives MS fatigue. The following definition of fatigue was recently proposed: "The decrease in physical and/or mental performance that results from changes in central, psychological, and/or peripheral factors" [30].

We aimed to validate the Fatigue Scale for Motor and Cognitive Functions (FSMC),[15] a frequently used fatigue scale among MS patients in Denmark, and to compare it with the already well-established Modified Fatigue Impact Scale (MFIS) (1998).

Cognition in MS: self-reported and objective measures

Cognitive impairment (CI) is frequent in people with MS. CI in MS patients typically affects memory, information processing speed, learning, and executive function, thus influences activities of daily living (ADL) and QoL[31, 32]. CI is the primary cause of unemployment in people with MS, being reported in seven to eight out of ten cases[16, 31, 33]. CI may progress as a sign of disease activity; its monitoring is also important when treating patients with immunomodulatory drugs that may induce progressive multifocal leukoencephalopathy (PML). Cognitive screening is thus valuable both as a means of assessment and as a guide for treatment[34, 35]. Prevalence studies have found cognitive impairment in approximately 50% of those afflicted by MS, based on performance below a chosen threshold (usually 1.5 SDs below average). Typically cross-sectional, such studies do not reflect long-term outcome[32]. However, patients with high premorbid cognitive reserve may not cross the threshold into impairment, despite the notable decline from previous function[36]. Given the prevalence and morbidity, there is a need for cost-effective screening tools for cognitive impairment that can longitudinally evaluate cognitive decline.

The Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) is a PRO that can be easily administered by either the patient (MSNQ-P) or an informant (MSNQ-I). It has been shown to have an acceptable reproducibility and to provide valid assessment of cognitive dysfunction in American, Argentinean, and Dutch populations.[37-40]

The objective of our study was to validate a Danish translation of the MSNQ, compared to formal neuropsychological testing as well as to the Symbol Digit Modalities Test (SDMT), and to test for construct validity with depression (BDI), and disability (EDSS/MSIS).

Symbol Digit Modalities Test (SDMT)

Cognitive impairment occurs even in the earliest stages of the disease, irrespective of disease duration. Cognitive deficits may develop independently from physical disability, even in cases of benign MS. There are reports of relapse with primary cognitive impairment.[31, 41-43] Nevertheless, cognitive disturbances have also been shown to correlate with functional status measured by the Expanded Disability Status Scale (EDSS), and the presence of cognitive decline may predict a more progressive disease course[42, 44, 45]. Different aspects of general cognitive functioning may impact intellectual disability, including information processing efficiency, verbal and visuospatial memory, executive functioning, attention, and visual perceptual processing - for which dedicated neuropsychological test batteries have been developed. Particularly, processing speed and visual memory seem to be most commonly affected[16, 32, 46].

If only five minutes are available for testing, the SDMT test is recommended in the Brief International Cognitive Assessment for MS (BICAMS) as the cognitive test of choice. This easily administered test measures processing speed and working memory, does not require trained personnel,[47, 48] and is an effective tool for detecting cognitive decline in clinical practice[49].

Using the SDMT in a few MS cohorts, natalizumab treatment has been shown to have a positive effect on cognition. The frequency of SDMT testing and follow-up varies in these studies: monthly, six-monthly, and annual examinations have been applied from 48 weeks to up to 2 years[44, 50-53].

Patients treated with natalizumab for CI may present with cognitive worsening as the first symptom of PML (a known adverse event in the SDMT); we use SDMT at our clinic immediately before the monthly natalizumab infusions as a rapid screening test for subclinical PML in JC-virus infected patients.[54, 55] However, a potential practice effect may complicate the interpretation of SDMT results, as patients who use the same SDMT every month gain familiarity with it.

Our study in the Thesis aimed to examine cognitive performance and practice effect on patients exposed to monthly testing with SDMT during natalizumab treatment of up to 35 months.

References

1. Neligan A, Hauser WA and Sander JW. The epidemiology of the epilepsies. *Handbook of clinical neurology* 2012; 107: 113-133. 2012/09/04. DOI: 10.1016/b978-0-444-52898-8.00006-9.
2. Smitherman TA, Burch R, Sheikh H, et al. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. *Headache* 2013; 53: 427-436. 2013/03/09. DOI: 10.1111/head.12074.
3. Bentzen J, Flachs EM, Stenager E, et al. Prevalence of multiple sclerosis in Denmark 1950--2005. *Multiple sclerosis (Houndmills, Basingstoke, England)*; 16: 520-525.
4. Confavreux C and Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain : a journal of neurology* 2006; 129: 606-616. 2006/01/18. DOI: 10.1093/brain/awl007.
5. Koch-Henriksen N, Laursen B, Stenager E, et al. Excess mortality among patients with multiple sclerosis in Denmark has dropped significantly over the past six decades: a population based study. *Journal of neurology, neurosurgery, and psychiatry* 2017; 88: 626-631. 2017/07/15. DOI: 10.1136/jnnp-2017-315907.
6. Smith AL, Cohen JA and Hua LH. Therapeutic Targets for Multiple Sclerosis: Current Treatment Goals and Future Directions. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics* 2017 2017/06/28. DOI: 10.1007/s13311-017-0548-5.
7. Compston A. *McAlpine's multiple sclerosis*. 4th ed. Philadelphia: Churchill Livingstone Elsevier, 2005, p.x, 982 p.
8. Dalton CM, Brex PA, Miszkiel KA, et al. Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. *Annals of neurology* 2002; 52: 47-53. 2002/07/12. DOI: 10.1002/ana.10240.
9. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of neurology* 2011; 69: 292-302. 2011/03/10. DOI: 10.1002/ana.22366.

10. Ebers GC. Natural history of primary progressive multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2004; 10 Suppl 1: S8-13; discussion S13-15. 2004/06/29.
11. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; 83: 278-286. 2014/05/30. DOI: 10.1212/wnl.0000000000000560.
12. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Annals of neurology* 2009; 66: 460-471. 2009/10/23. DOI: 10.1002/ana.21867.
13. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *The New England journal of medicine* 2017; 376: 209-220. 2016/12/22. DOI: 10.1056/NEJMoa1606468.
14. Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *The Lancet Neurology* 2009; 8: 254-260. 2009/02/10. DOI: 10.1016/s1474-4422(09)70021-3.
15. Penner IK, Raselli C, Stocklin M, et al. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2009; 15: 1509-1517. 2009/12/10. DOI: 10.1177/1352458509348519.
16. Rao SM, Leo GJ, Ellington L, et al. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology* 1991; 41: 692-696.
17. Rogers JM and Panegyres PK. Cognitive impairment in multiple sclerosis: evidence-based analysis and recommendations. *J Clin Neurosci* 2007; 14: 919-927.
18. Nixon R, Bergvall N, Tomic D, et al. No evidence of disease activity: indirect comparisons of oral therapies for the treatment of relapsing-remitting multiple sclerosis. *Advances in therapy* 2014; 31: 1134-1154. 2014/11/22. DOI: 10.1007/s12325-014-0167-z.
19. Kappos L, De Stefano N, Freedman MS, et al. Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing-remitting multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2016; 22: 1297-1305. 2015/11/21. DOI: 10.1177/1352458515616701.
20. Deshpande PR, Rajan S, Sudeepthi BL, et al. Patient-reported outcomes: A new era in clinical research. *Perspectives in clinical research* 2011; 2: 137-144. 2011/12/07. DOI: 10.4103/2229-3485.86879.
21. Rottoli M, La Gioia S, Frigeni B, et al. Pathophysiology, assessment and management of multiple sclerosis fatigue: an update. *Expert review of neurotherapeutics* 2017; 17: 373-379. 2016/10/13. DOI: 10.1080/14737175.2017.1247695.
22. Petersen RC, Smith GE, Waring SC, et al. Aging, memory, and mild cognitive impairment. *International psychogeriatrics* 1997; 9 Suppl 1: 65-69. 1997/01/01.
23. Carone DA, Benedict RH, Munschauer FE, 3rd, et al. Interpreting patient/informant discrepancies of reported cognitive symptoms in MS. *J Int Neuropsychol Soc* 2005; 11: 574-583.
24. Sonder JM, Bosma LV, van der Linden FA, et al. Proxy measurements in multiple sclerosis: agreement on different patient-reported outcome scales. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2012; 18: 196-201. 2011/09/13. DOI: 10.1177/1352458511417827.

25. Sonder JM, Holman R, Knol DL, et al. Analyzing differences between patient and proxy on Patient Reported Outcomes in multiple sclerosis. *J Neurol Sci* 2013; 334: 143-147. 2013/09/11. DOI: 10.1016/j.jns.2013.08.014.
26. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2003; 9: 219-227. 2003/06/20. DOI: 10.1191/1352458503ms904oa.
27. Minden SL, Frankel D, Hadden L, et al. The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2006; 12: 24-38. 2006/02/08. DOI: 10.1191/135248506ms1262oa.
28. Amato MP, Ponziani G, Rossi F, et al. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2001; 7: 340-344.
29. Krupp LB, Alvarez LA, LaRocca NG, et al. Fatigue in multiple sclerosis. *Archives of neurology* 1988; 45: 435-437.
30. Rudroff T, Kindred JH and Ketelhut NB. Fatigue in Multiple Sclerosis: Misconceptions and Future Research Directions. *Front Neurol* 2016; 7: 122. DOI: 10.3389/fneur.2016.00122.
31. Glanz BI, Healy BC, Rintell DJ, et al. The association between cognitive impairment and quality of life in patients with early multiple sclerosis. *J Neurol Sci*; 290: 75-79.
32. Rao SM, Leo GJ, Bernardin L, et al. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology* 1991; 41: 685-691.
33. Baumstarck-Barrau K, Simeoni MC, Reuter F, et al. Cognitive function and quality of life in multiple sclerosis patients: a cross-sectional study. *BMC Neurol* 2011; 11: 17.
34. Clifford DB, De Luca A, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *The Lancet Neurology* 2010; 9: 438-446.
35. Hellwig K and Gold R. Progressive multifocal leukoencephalopathy and natalizumab. *Journal of neurology* 2011; 258: 1920-1928.
36. Sumowski JF, Rocca MA, Leavitt VM, et al. Brain reserve against physical disability progression over 5 years in multiple sclerosis. *Neurology* 2016; 86: 2006-2009. 2016/05/11. DOI: 10.1212/wnl.0000000000002702.
37. Benedict RH, Munschauer F, Linn R, et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2003; 9: 95-101.
38. Benedict RH, Weinstock-Guttman B, Fishman I, et al. Prediction of neuropsychological impairment in multiple sclerosis: comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Archives of neurology* 2004; 61: 226-230.
39. Benedict RH and Zivadinov R. Reliability and validity of neuropsychological screening and assessment strategies in MS. *Journal of neurology* 2007; 254 Suppl 2: II22-II25.
40. O'Brien A, Gaudino-Goering E, Shawaryn M, et al. Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes. *Arch Clin Neuropsychol* 2007; 22: 933-948.
41. Achiron A and Barak Y. Cognitive impairment in probable multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry* 2003; 74: 443-446. 2003/03/18.

42. Banati M, Sandor J, Mike A, et al. Social cognition and Theory of Mind in patients with relapsing-remitting multiple sclerosis. *European journal of neurology* 2010; 17: 426-433. 2009/11/20. DOI: 10.1111/j.1468-1331.2009.02836.x.
43. Glanz BI, Holland CM, Gauthier SA, et al. Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2007; 13: 1004-1010. 2007/07/12. DOI: 10.1177/1352458507077943.
44. Portaccio E, Stromillo ML, Goretti B, et al. Natalizumab may reduce cognitive changes and brain atrophy rate in relapsing-remitting multiple sclerosis--a prospective, non-randomized pilot study. *European journal of neurology* 2013; 20: 986-990. 2012/10/13. DOI: 10.1111/j.1468-1331.2012.03882.x.
45. Zipoli V, Goretti B, Hakiki B, et al. Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2010; 16: 62-67. 2009/12/10. DOI: 10.1177/1352458509350311.
46. Benedict RH, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc* 2006; 12: 549-558.
47. Benedict RH, Duquin JA, Jurgensen S, et al. Repeated assessment of neuropsychological deficits in multiple sclerosis using the Symbol Digit Modalities Test and the MS Neuropsychological Screening Questionnaire. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2008; 14: 940-946.
48. Langdon DW, Benedict RH, Wicklein EM, et al. Reports of patients and relatives from the CogniCIS study about cognition in clinically isolated syndrome: what are our patients telling us? *Eur Neurol* 2013; 69: 346-351. 2013/05/03. DOI: 10.1159/000345698.
49. Van Schependom J, D'Hooghe M B, Cleynhens K, et al. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. *European journal of neurology* 2014; 21: 1219-e1272. 2014/05/23. DOI: 10.1111/ene.12463.
50. Holmen C, Piehl F, Hillert J, et al. A Swedish national post-marketing surveillance study of natalizumab treatment in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2011; 17: 708-719. 2011/01/14. DOI: 10.1177/1352458510394701.
51. Iaffaldano P, Viterbo RG, Paolicelli D, et al. Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis: a prospective, open-label, two years observational study. *PloS one* 2012; 7: e35843. 2012/05/05. DOI: 10.1371/journal.pone.0035843.
52. Kunkel A, Fischer M, Faiss J, et al. Impact of natalizumab treatment on fatigue, mood, and aspects of cognition in relapsing-remitting multiple sclerosis. *Frontiers in neurology* 2015; 6: 97. 2015/06/02. DOI: 10.3389/fneur.2015.00097.
53. Morrow SA, O'Connor PW, Polman CH, et al. Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2010; 16: 1385-1392. 2010/08/27. DOI: 10.1177/1352458510378021.
54. Berger JR. The clinical features of PML. *Cleveland Clinic journal of medicine* 2011; 78 Suppl 2: S8-12. 2011/12/14. DOI: 10.3949/ccjm.78.s2.03.
55. Sorensen PS, Bertolotto A, Edan G, et al. Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2012; 18: 143-152. 2012/02/09. DOI: 10.1177/1352458511435105.

Aims of the Thesis

I

Is the FSMC a valid tool for monitoring fatigue in Danish patients with Multiple Sclerosis?

Oervik MS, Sejbaek T (shared 1st), Penner IK, Roar M and Blaabjerg M. Validation of the fatigue scale for motor and cognitive functions in a Danish multiple sclerosis cohort. *Multiple sclerosis and related disorders*. 2017; 17: 130–4.

II

Does the self-reported questionnaire MSNQ reflect cognitive performance in Danish patients with multiple sclerosis?

Sejbæk T, Blaabjerg M, Sprogøe P, Ravnborg M. Reliability and Validity of a Danish Version of the Multiple Sclerosis Neuropsychological Screening Questionnaire. *International journal of MS care*. Selected for special issue and part of CME/CNE program 2017

III

How does practice effect influence frequent testing of cognition assessed by means of SDMT in patients with multiple sclerosis?

Roar M, Illes Z and Sejbaek T. Practice effect in Symbol Digit Modalities Test in multiple sclerosis patients treated with natalizumab. *Multiple sclerosis and related disorders*. 2016; 10: 116–22.

Additional Publications

I

Willis M, Pearson O, Illes Z, Sejbaek T, Nielsen C, Duddy M, Petheram K, Munster CV, Killestein J, Malmeström C, Tallantyre E and Robertson N. An observational study of alemtuzumab following fingolimod for multiple sclerosis. *Neurology(R) neuroimmunology & neuroinflammation* 2017; 4: e320. 2017/01/20. DOI: 10.1212/nxi.0000000000000320.

II

Andersen MR, Roar M, Sejbaek T, Illes Z and Grauslund J.Long-term structural retinal changes in patients with optic neuritis related to multiple sclerosis. *Clinical ophthalmology (Auckland, NZ)* 2017; 11: 1519–1525. 2017/09/02. DOI: 10.2147/opth.s142206.

III

Nielsen HH, Beck HC, Kristensen LP, Burton M, Csepany T, Simo M, Dioszeghy P, Sejbaek T, Grebing M, Heegaard NH and Illes Z. The Urine Proteome Profile Is Different in Neuromyelitis Optica Compared to Multiple Sclerosis: A Clinical Proteome Study. *PloS one* 2015; 10: e0139659. 2015/10/16. DOI: 10.1371/journal.pone.0139659.

IV

Illes Z, Sejbaek T and Csepany T. Alemtuzumab: Benefits and challenges of a new therapy in multiple sclerosis. *Ideggyogyaszati szemle* 2015; 68: 155–164. 2015/07/18.

Submitted Papers in Review

I

Real-life Persistence and Tolerability to Dimethyl Fumarate at Two Major Multiple Sclerosis Centers in Denmark. Sejbaek T, Nybo M, Petersen T, Illes Z. MS and Related Disorders

II

De- and remyelination-related proteins in the CSF of multiple sclerosis subtypes . Martin NA, Nawrocki A, Molnar V, Elkjaer ML, Thygesen EK, Palkovits M, Acs P, Sejbaek T, Nielsen HH, Hegedus Z, Sellebjerg F, Barbosa EGV, Alcaraz N, Gallyas Jr F, Svenningsen AF, Baumbach J, Lassmann H, Larsen MR, Illes Z. Journal of Neuroinflammation

III

Omics-based approach reveals complement-mediated inflammation in CLIPPERS

Blaabjerg M, Hemdrup AL, Drici L, Ruprecht K, Garred P, Höftberger R, Kristensen BW, Kondziella D, Sejbaek T, Hansen SWK, Nielsen HH, Jensen P, Meyer M, Paul F, Lassmann H, Larsen MR, Illes Z. Frontiers in Immunology.

IV

Assessment of Relative Importance of Disease Modifying Treatment Attributes in Multiple Sclerosis Patients. Sejbaek T, Bøgelund M, Johansen JL and Madsen KG. Patient Preference and Adherence

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Validation of the fatigue scale for motor and cognitive functions in a danish multiple sclerosis cohort

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ABSTRACT

Background: Our objective was to validate the Danish translation of the Fatigue Scale for Motor and Cognitive Functions (FSMC) in multiple sclerosis (MS) patients.

Materials and methods: A Danish MS cohort (n = 84) was matched and compared to the original German validation cohort (n = 309) and a healthy control cohort (n = 147). The Modified Fatigue Impact Scale (MFIS) was used as reference scale and Becks Depression Inventory-Fast Screen (BDI-FS) and Expanded Disability Status Scale (EDSS) for confounding factors. We assessed internal consistencies; convergent, divergent, and predictive validity; partial correlations correcting for depression; significant differences between the mean scores of the cohorts; and sensitivity and specificity with receiver operating characteristic (ROC) curves.

Results: Excellent internal consistencies for the total scale and subscales were found (α = 0.91–0.95). Strong positive correlations between the two fatigue scales implied high convergent validity (total scores: r = 0.851, $p < 0.01$). The two cohorts corresponded well when divided into subgroups (EDSS score; age; gender). Correcting for depression did not result in any significant adjustments of the correlations. The area under the curve (AUC) for the ROC curves represented excellent accuracy (Danish MS cohort, AUC = 0.9190; German MS cohort, AUC = 0.9034).

Conclusion: The Danish translation of the FSMC has a high convergent validity with another measure of fatigue as well as excellent internal consistency and accuracy. It is found to be an applicable and recommendable measure of fatigue in Danish MS patients.

1. Introduction

Multiple sclerosis (MS) is a disease characterised by numerous neurological deficits including sensory and motor problems. Fatigue is the most commonly reported subjective symptom (65–95%), and often found to be the most debilitating (40%) (Bakshi, 2003; Minden et al., 2006). Together with depression, fatigue have a higher negative impact on quality of life (QoL) than physical complaints like spasticity and weakness (Amato et al., 2001). Fatigue in MS patients differs from normal tiredness experienced by healthy individuals. It is more severe, disabling, and more likely to interfere with them meeting their responsibilities (Krupp et al., 1988). Not only is the symptom itself a great burden to the patients, but the treatment of fatigue also presents a challenge. A major challenge in dealing with fatigue is that the aetiology and pathophysiology behind the symptom remains unclear (Rottoli et al., 2016) and there is no common unified definition among researchers and clinicians. A recently published study tried to limit this problem of inconsistency, by proposing the following definition for fatigue: "*The decrease in physical and/or mental performance that results from changes in central, psychological, and/or peripheral factors*" (Rudroff et al., 2016).

Monitoring fatigue as a symptom in clinical practice is based on the patient's own perception, and is most frequently done through self-report questionnaires. Due to both cultural and linguistic differences among countries, it is important to both translate and validate questionnaires in the native language of a patient population. Even though a number of different fatigue scales has been presented, most are only validated in English. In this study we wanted to validate a frequently

Abbreviations: FSMC, The fatigue scale for motor and cognitive functions;; MFIS, The modified fatigue impact scale; BDI-FS, Becks depression inventory-fast screen; EDSS, Expanded disability status scale

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used fatigue scale among MS patients in Denmark, namely the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009), and compare with the already well-established Modified Fatigue Impact Scale (MFIS) (1998). Both scales provide the possibility to subdivide the symptoms into the two entities of motor and cognitive fatigue.

2. Material & methods

2.1. Ethics

All procedures were performed according to the Declaration of Helsinki and with permission from the Regional Committees on Health Research Ethics for Southern Denmark (Reference number: S-20140034). The study was also approved by Danish Data Protection Agency (Reference number: 14/8330).

2.2. Participants

The study populations consisted of a Danish MS cohort (n = 84), a German MS cohort (n = 309), and a German healthy controls cohort (n = 147).

The Danish patient group was recruited, after written and oral informed consent, from the MS clinic at Odense University Hospital in 2014.

Inclusion criteria were: i) Clinically definite MS diagnosed by a specialist in Neurology according to the revised 2010 McDonald criteria (Polman et al., 2011), ii) age > 18 years, and iii) Danish as native language.

Exclusion criteria were: i) Other neurological diseases, ii) history of developmental disorders or other learning disability, iii) previous or present psychiatric diagnosis that is unlikely to be part of the patients' MS, iv) alcohol or drug abuse, and v) corticosteroids treatment within the last 4 weeks before evaluation. Information on age, gender, and Expanded Disability Status Scale (EDSS) (Kurtzke, 2015) score were also gathered.

All Danish study subjects completed the FSMC, the MFIS, and the Becks Depression Inventory-Fast Screen (BDI-FS) during a visit to the MS clinic.

2.3. Scales

All scales are self-evaluation questionnaires constructed as Likert scales, with 1–5 points per item for the FSMC, 0–4 points per item for the MFIS, and 0–3 points per item for the BDI-FS.

The FSMC consists of 20 items, with a subdivision of 10 motor and 10 cognition focused items. Cut-off values for grading of fatigue were based on the original validation data (Penner et al., 2009). A score of ≥ 43 equals mild, ≥ 53 equals moderate, and ≥ 63 equals severe fatigue. The total possible score ranges from 20 to 100 points. Cut-off values for the cognitive subscale were ≥ 22 for mild, ≥ 28 for moderate, and ≥ 34 for severe cognitive fatigue. For the motor subscale: ≥ 22 for mild, ≥ 27 for moderate, and ≥ 32 for severe motor fatigue (Penner et al., 2009).

The MFIS consists of 21 items, where 9 are related to motor, 10 to cognition, and 2 to psychosocial aspects of fatigue. The cut-off value defining fatigue related to MS is 38 points (Flachenecker et al., 2002), and the total possible score is between 0 and 84 points.

For assessment of depression we used BDI-FS. The scale consists of 7 items and cut-off values for interpretation are provided, where 0–4 points equals minimal depression, 4–8 equals mild, 9–12 equals moderate, and 10–21 equals severe (Smarr and Keefer, 2011).

2.4. Statistical analysis

Statistical validation was based on the recommendations of Bland and Altman (Bland and Altman, 2002).

Descriptive statistics were calculated for mean age, gender distribution, and mean EDSS score. The distribution of fatigue severity was calculated for each of the cohorts.

Due to the large sample size, manual inspection of box plots was performed to evaluate Gaussian distribution. Based on this, the data did not deviate from a normal distribution, and parametric tests were applied.

Cronbach's alpha was used for calculating internal consistency. Good consistency was defined as $\alpha \geq 0.8$.

Validity of the content was based on calculations on convergent and divergent validity. For convergent validity, we performed bivariate correlation analyses between the FSMC and the MFIS, both total and subscales. Divergent validity was assessed through correlations between fatigue scales and i) BDI-FS and ii) EDSS scores. Pearson correlation coefficient was used to calculate the correlations between the FSMC and MFIS. The correlations between the fatigue scales and the BDI-FS and EDSS score was calculated by the same method, as well as partial correlations correcting for the possible confounding effect of depression.

Predictive validity was calculated by comparing the cohorts through unpaired *t*-tests. First, we divided the patients into subgroups based on i) EDSS score (≤ 3 points for mild disability; 3.5–6 points for moderate disability; ≥ 6.5 points for severe disability), ii) age (10 year-intervals), and iii) gender. Next, we compared matched subgroups from the two MS cohorts and calculated the statistical significance.

The statistical significance of mean scores of individual items and of the total sums in both scales were estimated using two-sampled *t*-tests with unequal variances and post-hoc Bonferroni correction (for FSMC: $p < 0.0025$; for FSMC total and subscales: $p < 0.0167$; for MFIS: $p < 0.0024$; for MFIS total and subscales: $p < 0.0125$).

Moreover, we calculated the sensitivity and specificity for different cut-off values of the FSMC using MFIS as reference variable. Receiver operating characteristic (ROC) curves were plotted for these numbers.

The statistical analysis was done using STATA 14.0 and GraphPad PRISM 7. All p-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics

The study cohorts were well-matched in age, gender distribution, and mean EDSS score (Table 1). Even though the Danish cohort (n = 84) was smaller than the German (n = 309), they had a similar distribution when subdividing into the different fatigue severities according to the cut-off values (Table 1).

3.2. Reliability of the FSMC

Internal consistency of the whole questionnaire was calculated and compared to the original validation paper (Penner et al., 2009). In the Danish patient group; $\alpha = 0.95$ for the total scale, $\alpha = 0.93$ for the cognitive subscale, and $\alpha = 0.91$ for the motor subscale. None of the Cronbach's alpha values with missing item showed a higher value, indicating that removing any of the questions, would not increase the internal consistency of the questionnaire.

3.3. Validity of the FSMC

The two fatigue scales and related subscales correlated well. The cognitive subscales ($r = 0.8521$, $p < 0.0001$) as well as the motor subscales ($r = 0.774$, $p < 0.0001$) had strong positive correlation coefficients, concluding with a high convergent validity (Table 2).

Except from the cognitive subscales, all scales including subscales showed slightly weak, but significant, correlations with depression through the BDI-FS score (Table 3). Disability measured by EDSS scores showed the same trend; however, with a somewhat stronger correlation

Table 1
Demographics of the study cohorts.

	Danish cohort	German cohort	Healthy controls
N	84	309	147
Mean age (SD)	51.1 (9.4)	43.4 (9.9)	41.7 (12.9)
Gender			
– Female, N (%)	58 (69)	206 (67)	92 (63)
– Male, N (%)	26 (31)	103 (33)	55 (37)
EDSS (SD)	3.43 (1.8)	3.68 (1.2)	–
Degree of fatigue			
– Mild, N (%)	11 (9.5)	48 (15.5)	13 (8.8)
– Moderate, N (%)	15 (17.9)	59 (19.1)	6 (4.1)
– Severe, N (%)	51 (60.7)	153 (49.5)	2 (1.4)

Note: N, number of subjects; SD, standard deviation; %, percentages.

Table 2
Correlations between the fatigue scales in the Danish cohort.

	FSMC_M	MFIS_C	MFIS_M	MFIS_PS	MFIS_T
FSMC_C	0.7469**	**0.8521****	0.5364**	0.6565*	0.7779**
FSMC_M		0.6669**	**0.774****	0.7532**	0.8138**
FSMC_T		0.8154**	0.6975**	0.7527**	**0.851****

Note: Pearson correlation, 2-tailed, FSMC, Fatigue Scale for Motor and Cognitive Functions; MFIS, Modified Fatigue Impact Scale; _C, cognitive subscale; _M, motor subscale; _PS, psychosocial subscale; _T, total score of the scale.
** $p < .01$.

Table 3
Correlations and partial correlations controlling for depression shown in parentheses between fatigue scales and confounding factors in the Danish cohort.

	BDI-FS	EDSS
FSMC_C	0.1854	0.0581 (0.0469)
FSMC_M	0.3125**	**0.3526**** (**0.3504****)
FSMC_T	0.2645*	0.2153* (0.2057)
MFIS_C	0.2054	0.07032 (0.0582)
MFIS_M	0.2857**	**0.5291**** (**0.5338****)
MFIS_PS	0.3303**	0.2927** (0.2878**)
MFIS_T	0.286**	0.3341** (0.3298**)

Note: Pearson correlation, 2-tailed, FSMC, Fatigue Scale for Motor and Cognitive Functions; MFIS, Modified Fatigue Impact Scale; _C, cognitive subscale; _M, motor subscale; _PS, psychosocial subscale, _T, total score of the scale; BDI-FS, Becks Depression Inventory-Fast Screen; EDSS, Expanded Disability Status Scale.
* $p < .05$.
** $p < .01$.

with the motor subscale of the MFIS ($r = 0.5291$, $p < 0.0001$) (Table 3). Partial correlations for depression did not result in any significant adjustments in the correlations (Table 3). No significant correlations were found with age or gender.

When considering predictive validity, the most severely disabled patients (EDSS ≥ 6.5) reported a higher fatigability in motor functions (Table 4). However, they did not report higher cognitive fatigability than less disabled patients, rather lower than patients with EDSS score 3.5–6. When comparing the Danish with the German MS cohort, there was only one significantly different mean score between EDSS groups (MFIS cognitive subscale, EDSS 3.5–6, $p = 0.0117$). The rest of the subgroups matched well with their corresponding group (Table 4).

When subdividing based on gender, we found two significant differences between the two cohorts (FSMC motor subscale, female, $p = 0.0225$; MFIS cognitive subscale, female, $p = 0.0331$). No significant differences were found between the age groups, though we did not analyse the youngest (20–29 years; Danish cohort, $n = 0$; German cohort, $n = 30$) and the oldest (≥ 70 years; Danish cohort, $n = 4$; German cohort, $n = 0$) groups, due to low numbers (Table 4).

When performing multiple *t*-tests based on mean scores of single items and total scores, we found no items in the FSMC and only 3 out of 21 items in the MFIS to be significantly different (Fig. 1).

3.4. Sensitivity and specificity

Based on the cut-off value for mild fatigue (43 points) (Penner et al., 2009), the sensitivity was 100% and the specificity was 36%. With a cut-off of 53 points (moderate fatigue), the sensitivity was decreased to 98% whereas the specificity was increased to 61%. Finally, with a cut-off of 63 points (severe fatigue), the sensitivity further decreased to 84%, but the specificity was increased to 86%. Virtually equivalent numbers for the respective cut-off values were found when analysing the German MS cohort as well. Plotting of ROC curves for the Danish cohort resulted in an area under the curve (AUC) of 0.9190 (95% CI: 0.85156–0.98645), whereas the corresponding number in the German cohort was AUC = 0.9034 (95% CI: 0.86930–0.93752), representing an excellent accuracy (defined as > 0.9) of the test (Fig. 2).

4. Discussion

Validation of questionnaires in the native language of a given patient population is important due to possible cultural and linguistic differences. The present study validated the FSMC in a Danish MS cohort and compared it to the already well-accepted MFIS and the German study cohorts from the original validation of the scale (Penner et al., 2009).

The two MS cohorts were well-matched in terms of gender and EDSS

Table 4
Mean scores with standard deviations of the Danish cohort based on subgroups.

	FSMC_C	FSMC_M	FSMC_T	MFIS_C	MFIS_M	MFIS_PS	MFIS_T
EDSS							
0–3	31.12 (± 10.58)	31.86 (± 10.04)	62.98 (± 20.04)	17.90 (± 8.62)	16.10 (± 7.65)	3.31 (± 2.02)	37.31 (± 17.09)
3.5–6	33.97 (± 8.48)	36.31 (± 7.93)	70.28 (± 14.54)	20.63 (± 7.13)	21.10 (± 7.04)	3.66 (± 1.84)	45.38 (± 14.09)
≥ 6.5	28.90 (± 9.45)	38.10 (± 6.94)	67.00 (± 15.00)	16.00 (± 7.27)	25.10 (± 5.86)	4.30 (± 1.42)	45.40 (± 11.46)
Age							
20–29	–	–	–	–	–	–	–
30–39	29.40 (± 9.94)	33.20 (± 12.66)	62.60 (± 22.07)	14.80 (± 8.44)	17.00 (± 9.37)	3.40 (± 2.41)	35.20 (± 18.95)
40–49	30.52 (± 10.25)	32.59 (± 9.85)	63.10 (± 18.87)	17.66 (± 8.59)	17.86 (± 8.94)	3.55 (± 2.08)	39.07 (± 16.97)
50–59	34.55 (± 9.15)	36.58 (± 6.84)	71.13 (± 14.78)	20.94 (± 7.04)	21.26 (± 5.76)	3.71 (± 1.64)	45.90 (± 12.55)
60–69	30.30 (± 9.50)	31.70 (± 9.01)	62.00 (± 16.27)	18.00 (± 5.85)	16.80 (± 8.04)	2.70 (± 1.57)	37.50 (± 14.05)
≥ 70	32.50 (± 10.91)	38.25 (± 10.90)	62.00 (± 21.05)	20.75 (± 12.31)	21.75 (± 8.02)	5.00 (± 1.41)	47.50 (± 21.67)
Gender							
Female	33.02 (± 20.50)	34.71 (± 28.80)	67.72 (± 32.13)	19.40 (± 7.48)	19.48 (± 7.00)	3.72 (± 1.81)	42.60 (± 13.96)
Male	29.54 (± 9.36)	33.38 (± 9.38)	62.92 (± 17.41)	17.19 (± 9.03)	18.15 (± 9.56)	3.19 (± 2.06)	38.54 (± 19.26)

Note: FSMC, Fatigue Scale for Motor and Cognitive Functions; MFIS, Modified Fatigue Impact Scale; _C, cognitive subscale; _M, motor subscale; _PS, psychosocial subscale; _T, total score of the scale; EDSS, Expanded Disability Status Scale.

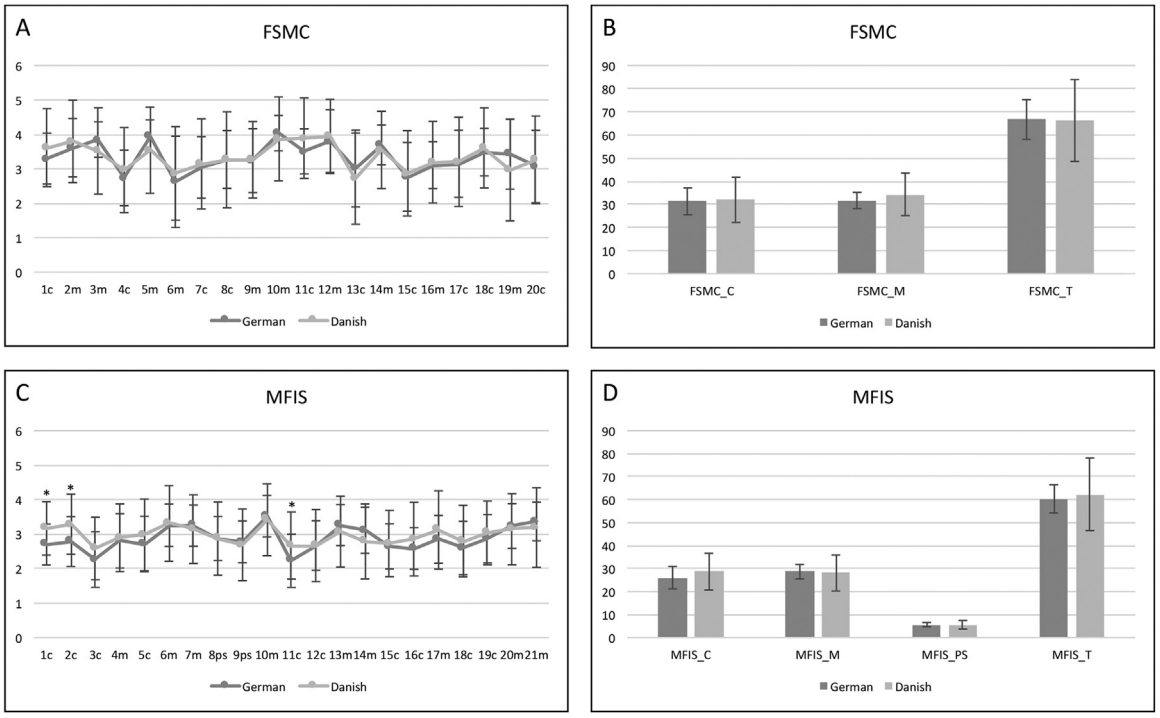

Fig. 1. A comparison of single questions and total scores with standard deviations (SD). *Note:* Mean values of each item and the total scales and subscales with standard deviations of the Danish (n = 84) and the German (n = 309) cohort; *significant after post-hoc Bonferroni correction; FSMC, Fatigue Scale for Motor and Cognitive Functions; MFIS, Modified Fatigue Impact Scale; _C, cognitive subscale; _M, motor subscale; _PS, psychosocial subscale; _T, total score of the scale. Each item is expressed with the name of the scale followed by the number of the item and a letter referring to m: motor, c: cognition, or ps: psychosocial. Figure A: FSMC, single items; figure B: FSMC, total scores; figure C: MFIS, single items; figure D: MFIS, total scores.

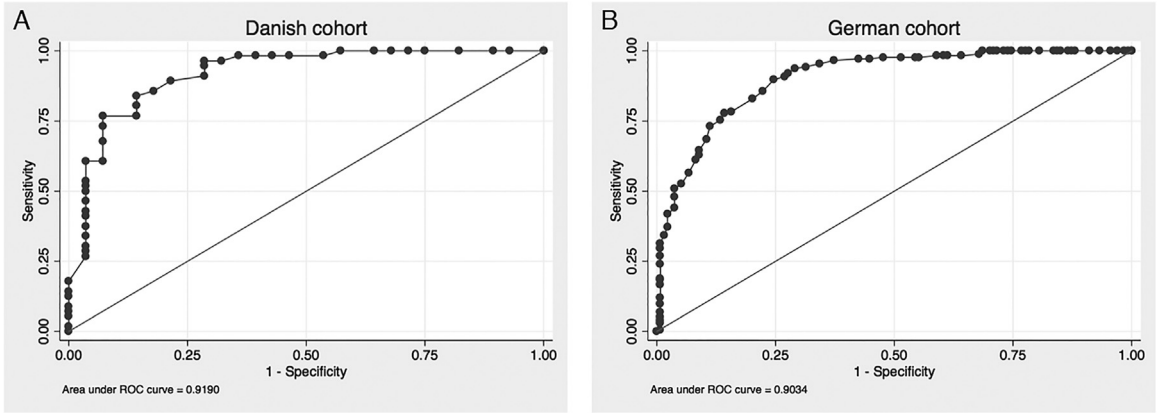

Fig. 2. Receiver operating characteristic (ROC) curves. *Note:* ROC curves for the total scale of the Fatigue Scale for Motor and Cognitive Functions (FSMC) plotted separately for the Danish (A) and the German (B) cohorts using the Modified Fatigue Impact Scale (MFIS) as a reference variable.

score, except from a light skew of the Danish cohort towards more severely disabled. This incoherence is likely due to the Danish patient cohort on average being 10 years older, corresponding to a probable longer disease duration.

Excellent internal consistencies were found, identical to the ones found in the original validation (Penner et al., 2009), expressing high interrelatedness of the items and/or a homogeneity of the whole scale and subscales. However, the optimal value of alpha has been a point of discussion in statistics, and some suggest that high values (> 0.90) may indicate redundancies. (Tavakol, 2011).

Our results demonstrate a high convergent validity, with strong positive correlations between the two fatigue scales and their subscales. As expected, both motor subscales showed significant correlations to the EDSS score, though only at a weak to moderate level. There were no correlations between the cognitive subscales and the BDI-FS score. Neither did any of the fatigue scales or subscales correlate with age or gender.

Interestingly, the most severely disabled patients (EDSS > 6.5), had a lower score on the cognitive subscale compared with those less disabled. Likely, this is due to a smaller sample size in these patients. Two significant differences were found in the gender group and one found in the EDSS group. This may be a result of the known statistical problem of multiple testing and false positives (type I error). The same type of error may apply to the comparisons of mean values between cohorts, as some questions in the MFIS are significantly different. However, this may as well suggest a better fit of the FSMC to the Danish MS population than the MFIS.

The calculated sensitivity and specificity showed the optimal results for the cut-off values 53 and 63 points, depending on whether you choose to accept a very high sensitivity on the expense of a moderate

specificity or a decently high sensitivity and specificity, respectively. We chose the listed cut-offs based on maximal sensitivity and very low specificity in the first value (43 points) and decreasing sensitivity in the last (63 points). When comparing the sensitivity and specificity calculated for the different cut-off values in the Danish and German cohorts, the numbers were virtually equal, suggesting application of the original cut-off values for Danish patients. The accuracy of the test measured by the area under the curve is excellent, representing high reliability in terms of separating the cohort being tested into those with and those without fatigue (Hajian-Tilaki, 2013). A possible bias lies in the reliability of the MFIS to distinguish the presence of the symptom.

There are some limitations to our study. First, we had no healthy Danish control group. Second, we were not able to check for test-retest reliability. Third, the MFIS is not validated in Denmark. Future studies may consider validating this scale in Denmark.

In conclusion, the FSMC has a high convergent validity with another measure of fatigue as well as excellent internal consistency and accuracy. It is found to be an applicable and recommendable measure of fatigue in Danish MS patients.

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Conflicts of interest and sources of funding statement

There are no conflicts of interest to declare in this study.

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References

Amato, M.P., Ponziani, G., Rossi, F., Liedl, C.L., Stefanile, C., Rossi, L., 2001. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. Mult. Scler. 7, 340–344.
Bakshi, R., 2003. Fatigue associated with multiple sclerosis: diagnosis, impact and management. Mult. Scler. 9, 219–227.
Bland, J.M., Altman, D.G., 2002. Statistics notes: validating scales and indexes. BMJ 324, 606–607.
Flachenecker, P., Kumpfel, T., Kallmann, B., Gottschalk, M., Grauer, O., Rieckmann, P., et al., 2002. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Mult. Scler. 8, 523–526.
Hajian-Tilaki, K., 2013. Receiver Operating Characteristic (ROC) curve analysis for medical diagnostic test evaluation. Casp. J. Intern. Med. 4, 627–635.
Krupp, L.B., Alvarez, L.A., LaRocca, N.G., Scheinberg, L.C., 1988. Fatigue in multiple sclerosis. Arch. Neurol. 45, 435–437.
Kurtzke, J.F., 2015. Further to the origin of EDSS (Response to: l. Kappos et al.: "on the origin of Neurostatus" multiple sclerosis and related disorders 2015; 4: 186). Mult. Scler. Relat. Disord. 4, 186.
Minden, S.L., Frankel, D., Hadden, L., Perloffp, J., Srinath, K.P., Hoaglin, D.C., 2006. The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. Mult. Scler. 12, 24–38.
Penner, I.K., Raselli, C., Stocklin, M., Opwis, K., Kappos, L., Calabrese, P., 2009. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult. Scler. 15, 1509–1517.
Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., et al., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69, 292–302.
Rottoli, M., La Gioia, S., Frigeni, B., Barcella, V., 2016. Pathophysiology, assessment and management of multiple sclerosis fatigue: an update. Expert Rev. Neurother.
Rudroff, T., Kindred, J.H., Ketelhut, N.B., 2016. Fatigue in multiple sclerosis: misconceptions and future research directions. Front. Neurol. 7, 122.
Smarr, K.L., Keefer, A.L., 2011. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Res. (Hoboken). 63 (Suppl 11), S454–S466.
Tavakol, M.D.R., 2011. Making sense of Cronbach's alpha. Int. J. Med. Educ. 2, 53–55.

Manuscript II (MSNQ, Proof IJMSC)

CME/CNE ARTICLE • 2018 SERIES • NUMBER 1

Reliability and Validity of a Danish Version of the Multiple Sclerosis Neuropsychological Screening Questionnaire

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CME/CNE Information

Activity Available Online:
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Target Audience:
The target audience for this activity is physicians, physician assistants, nursing professionals, and other health-care providers involved in the management of patients with multiple sclerosis (MS).

Learning Objectives:
1) Describe cognitive impairment in MS and understand differences between patient-reported outcome scales and neuropsychological testing.
2) Understand the design of validation studies and be aware that results from translated and unvalidated patient-reported outcome scales may result in bias.

Accreditation Statement:

In support of improving patient care, this activity has been planned and implemented by the Consortium of Multiple Sclerosis Centers (CMSC) and Delaware Media Group. CMSC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Laurie Scudder, DNP, NP, has served as reviewer for this activity. She has disclosed no relevant financial relationships.

Tobias Sejbæk, MD, has received honoraria from lectures at a Biogen symposium; has performed contracted research as principal investigator of a phase 4 trial with support from Biogen; has served on the scientific advisory boards of Novartis, Biogen, Teva, Merck, and Roche; and has received travel funding or speaker honoraria from Biogen, Teva, and Novartis.

Morten Blaabjerg, MD, PhD, has received honoraria from lectures at a symposium organized by Biogen Denmark.

Pippi Sprogøe, MSc, has disclosed no relevant financial relationships.

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Background: *More than half of all patients with multiple sclerosis (MS) acquire cognitive impairment as part of their disease progression. Because cognitive dysfunction adds substantially to disability and coping strategies, a cost-effective screening tool is needed for cognitive impairment. The Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) has previously shown good validity in American, Argentinean, and Dutch MS cohorts. We sought to test reliability and validity of a Danish translation of the MSNQ compared with formal neuropsychological testing, and measures of depression and disability, and to compare self-reported cognition with Symbol Digit Modalities Test (SDMT) results.*

Methods: *Of 126 patients with MS and their informants tested with the MSNQ, 77 also underwent formal neuropsychological testing. All patients were tested with the SDMT and assessed clinically using the Expanded Disability Status Scale and MS Impairment Scale.*

Results: *The test-retest reliability of the MSNQ-P was significant (R^2 = 0.79, P < .0001). R^2 of informants (MSNQ-I) and patients (MSNQ-P) was much lower (R^2 = 0.22, P < .0001). Compared with formal neuropsychological testing, the MSNQ-P and MSNQ-I performed poorly, with no correlation to individual neuropsychological tests, combined neuropsychological tests, or disability scores (Expanded Disability Status Scale and MS Impairment Scale). Depression/anxiety (Beck Depression Inventory) showed a weak linear relationship (R^2 = 0.25, P < .0001), suggesting that the MSNQ-P measures these items more than the cognitive abilities of the patients.*

Conclusions: *This study does not support use of the MSNQ as a sensitive or valid screening tool for cognitive impairment in Danish patients with MS.* ***Int J MS Care*. 2018;XX:XXX-XXX.**

Cognitive impairment is a common problem in multiple sclerosis (MS), occurring in approximately 50% of patients. It typically involves memory, information-processing speed, learning, and executive function and, thereby, affects activities of daily living and quality of life.[1,2] Moreover, cognitive impairment is often the primary cause of unemployment, reported in 70% to 80% of all patients with MS.[1,3,4] Cognitive impairment may prove to be the only parameter in a few patients with MS and especially in patients with MS treated with immunomodulatory drugs that can induce progressive multifocal leukoencephalopathy. Cognitive screening is, thus, incredibly valuable as a means of assessment and as a guide for treatment.[5,6] Considering the prevalence and morbidity, there is a need for cost-effective screening tools for cognitive impairment in MS.

The best-validated fast screening test in patients with MS is the Symbol Digit Modalities Test (SDMT). This test is easy to administer and correlates well with cognitive impairment as measured by other standardized neuropsychological batteries assessing multiple functions and brain atrophy.[7] The SDMT, however, addresses only a fraction of the cognitive functions, such as process speed and visuospatial and working memory.[8,9]

The Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) is a brief patient-reported outcome scale by either the patient (MSNQ-P) or the informant (MSNQ-I) and is easy to administer. It has previously been shown to have acceptable reproducibility and to provide valid assessment of cognitive dysfunction in American, Argentinean, and Dutch populations. In contrast to the SDMT, the MSNQ can provide information about self- and informant-perceived cognitive dysfunction.[10-13]

The objective of this study was to validate a Danish translation of the MSNQ compared with formal neuropsychological testing and with the SDMT and measures of depression and disability.

Methods

Ethics

All the procedures were performed according to the Declaration of Helsinki and with permission from the Danish Data Protection Agency (14/8330).

Translation of MSNQ

The MSNQ was translated by a bilingual translator from English to Danish and then was translated from Danish to English by another translator to correct for any linguistic corrections or oversights.

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Study Population

We studied 126 patients diagnosed as having MS in the Department of Neurology, Odense University Hospital (Odense, Denmark), over 7 consecutive years (January 1, 2000, through December 31, 2006). The inclusion criteria were 1) a diagnosis of MS according to the McDonald criteria,[14] 2) an informant with face-to-face contact with the patient three or more times a week, 3) age older than 18 years, 4) Danish as the first language, and 5) informed consent. The exclusion criteria were 1) neurologic deficits not related to MS, 2) a history of developmental disorders or other learning disabilities, 3) previous or present psychiatric disease that is unlikely to be part of the patient's MS, 4) alcohol or drug abuse, and 5) corticosteroid treatment in the 4 weeks before evaluation. Informants were selected by the following criteria: closest family or friend with whom the patient lives or has at least three weekly contacts, in the following prioritized rank: spouse, father/mother, daughter/son, friend/closest family.

Application of MSNQ, SDMT, and Neuropsychological Testing

Patients and their respective informants were carefully given standardized instructions on how to fill out the MSNQ[10] and the Beck Depression Inventory (BDI)[15] during each contact. Patients completed questionnaires in the department, and a neurologist (M.B. or T.S.) assessed clinical deficits by means of the MS Impairment Scale (MSIS),[16,17] the Expanded Disability Status Scale (EDSS),[18] and the SDMT.[19,20]

Informants completed the MSNQ-I during the visit or within a few weeks. The first 77 patients examined were chosen for neuropsychological testing, which occurred a few weeks after contact with the neurologist. The test battery comprised the following tests: the Rey Auditory Verbal Learning Test, the Trail Making Test B, the Wisconsin Card Sorting Test, the Boston Naming Test, and Digit-Symbol Coding. A *z* score of the combined neuropsychological tests was calculated from the test results, and a *z* score less than –1.5 SD was used as the cutoff point to diagnose true cognitive impairment.

Based on earlier studies, a cutoff score of 26 points or greater on the MSNQ-I and the MSNQ-P was chosen as a sign of cognitive impairment.[10,12,13,21,22] Forty-four patients were retested (Figure 1) to investigate the test-retest variability of the MSNQ-I and the MSNQ-P.

Statistical Methods

Z scores were based on sex- and age-matched controls. *Z* scores could not be calculated for nine patients due to either missing age-matched normal values (patients >60 years old) or incomplete neuropsychological testing. Three informants did not return the MSNQ-I (Figure 1). Statistical analyses were performed using GraphPad PRISM 7 (GraphPad Software Inc, La Jolla, CA). Because data were not distributed normally, nonparametric statistics were used.

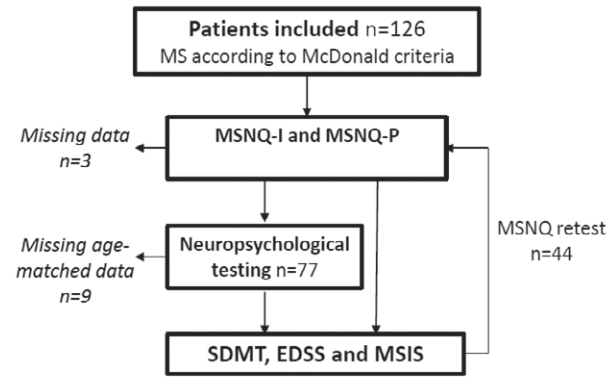

***Figure 1.* Study flowchart**

A total of 126 patients with multiple sclerosis (MS) were included in the study, and 77 of these underwent formal neuropsychological testing. Data from nine patients were incomplete due to failure to complete the neuropsychological test battery. Moreover, three informants did not return Multiple Sclerosis Neuropsychological Screening Questionnaire–Informant (MSNQ-I). All included patients were assessed for disability using Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Impairment Scale (MSIS) and performed Symbol Digit Modalities Test (SDMT). A total of 44 patients were retested with MNSQ-Patient (MNSQ-P) to determine test-retest reliability.

Results

Demographics and Comparison of Subgroups

Comparing patients who underwent neuropsychological testing (n = 77) with those who did not (n = 49), we found no differences in demographics in relation to age, disease duration, and disability as measured by the EDSS and the MSIS. There were also more men in the neuropsychological group (43%) compared with in the group that was not tested by a neuropsychologist (26%) ($P < .05$) (Table 1).

Test-Retest of MSNQ-P and Correlation Between MSNQ-I and MSNQ-P

The squared test-retest correlation of the MSNQ-P was $R^2 = 0.79$ ($P < .0001$) (Figure 2A) and the squared correlation of the informants (MSNQ-I) and patients (MSNQ-P) was low but significant ($R^2 = 0.22$, $P < .0001$) (Figure 2B).

Squared Correlation Between MSNQ and Neuropsychological Tests and BDI

When correlating the MSNQ-I or the MSNQ-P (greater than the cutoff score of 26 points) with the *z*

Table 1. Baseline demographic characteristics of the 126 study participants

	Neuropsychological testing		
Characteristic	Yes (n = 77)	No (n = 49)	*P* value
Age, mean (range), y	45.6 (26-71)	48.4 (28-68)	.08
Sex, M:F, %	43:57	26:74	.03
Disease duration, mean (range), y	7.8 (4-10)	7.2 (4-10)	.06
EDSS score, mean (range)	2.8 (0-7.0)	3.4 (1-8.0)	.11
MSIS score, mean (range)	22.1 (0-86)	21.9 (0-103)	.72

Abbreviations: EDSS, Expanded Disability Status Scale; MSIS, MS Impairment Scale.

score of the complete neuropsychological test battery, we found no significant squared correlation with either scale (MSNQ-P: R^2 = 0.0084, P = .457; MSNQ-I: R^2 = 0.0345, P = .1388) (Figure 3). Neither did the MSNQ-I and the MSNQ-P correlate with the individual neuropsychological tests (Table 2). We found low sensitivity and specificity of the MSNQ-P (21.4% and 76%, respectively) and the MSNQ-I (33% and 65.5%, respectively). Both scales did, however, correlate to BDI scores (MSNQ-P: R^2 = 0.25, P < .0001; MSNQ-I: R^2 = 0.197, P < .0001 [data not shown]).

Squared Correlation Between MSNQ and Disability Scores

To investigate whether there is a correlation between cognitive dysfunction measured by the MSNQ and disability, we compared MSNQ-I with EDSS and MSIS scores. We found no squared correlation to either objective disability measure (EDSS: R^2 = 0.0036, P = .5; MSIS: R^2 = 0.0001, P = .89 [data not shown]).

Correlation of SDMT and Neuropsychological Testing

As a positive control for bedside neuropsychological testing in patients with MS, we also tested the squared correlation between the well-established SDMT and the total neuropsychological test panel. As expected, this squared correlation was highly significant (R^2 = 0.68, P < .0001) (Figure 4). When correlated to the individual neuropsychological tests, we found the best squared correlations to Digit-Symbol Coding and the Trail Making Test B. The SDMT also correlated to the Rey Auditory Verbal Learning Test and the Wisconsin Card Sorting Test but not to the Boston Naming Test (Table 2).

Discussion

The results of the present study show that a Danish translation of the MSNQ, despite good test-retest reliability, has no statistically significant correlation to cognitive impairment found on standard neuropsychological testing. This is in contrast to validation studies in other languages.[12,13,21,22] When using the now well-established SDMT scale, we did, however, find a highly significant correlation with the neuropsychological test battery, demonstrating the superiority of this scale in establishing the presence of cognitive impairment in MS.[23-26] Several factors may explain the low sensitivity and specificity of the MSNQ in the present study. First, we used an MSNQ cutoff score greater than 26, which is the cutoff score used in the original validation.[10] Other studies have used different cutoff values to achieve higher sensitivity and specificity, and the optimal cutoff score seems to change from study to study.[13,22,27] Using other cutoff points did not increase the sensitivity or specificity in the present population.

Second, compared with most of the earlier MSNQ validation studies performed,[13,22,27] the present cohort demonstrated a shorter disease duration (mean, 7.8 years), a lower EDSS score (mean, 2.8), and fewer cognitively impaired patients (13 of 77). A screening tool for cognitive impairment should, however, be relevant also in younger MS cohorts with shorter disease durations, and, when using the SDMT in the present cohort, we

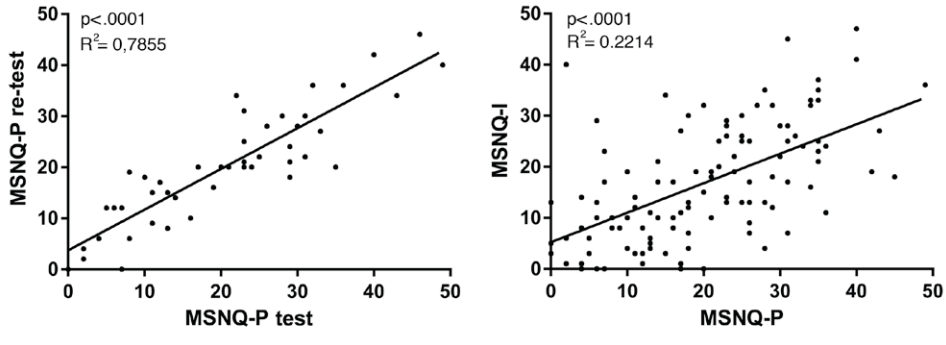

Figure 2. Linear fit regression of Multiple Sclerosis Neuropsychological Screening Questionnaire–Patient (MSNQ-P) and MSNQ-Informant (MSNQ-I)

A, MSNQ-P scores for test-retest linear fit regression (n = 44). Each dot indicates the MSNQ-P score in the test-retest (variability within same patient). B, MSNQ-P/MSNQ-I linear fit regression (n = 116). Each dot indicates an MSNQ-P/MSNQ-I score (variability between patient and informant).

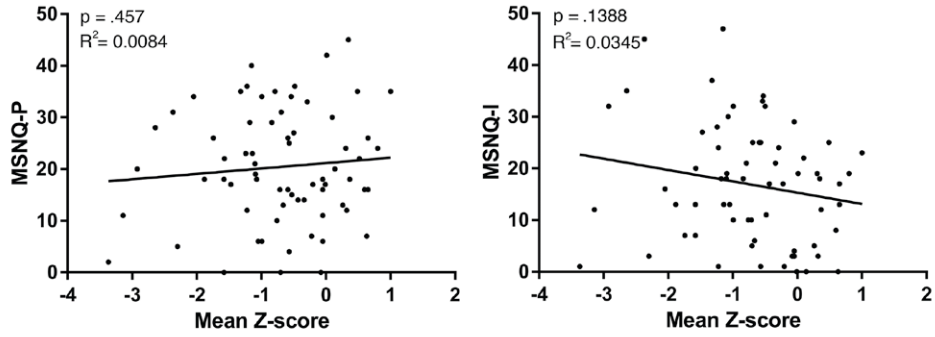

***Figure 3.* Linear fit regression of Multiple Sclerosis Neuropsychological Screening Questionnaire–Patient (MSNQ-P) or MSNQ-Informant (MSNQ-I) and neuropsychological test battery**

Linear fit regressions between MSNQ-P (A) and MSNQ-I (B) scores and mean z scores of all the neuropsychological tests (n = 68). No correlation was found with z scores and MSNQ-P or MSNQ-I.

data. We found that the MSNQ-I and the MSNQ-P correlated significantly with BDI scores. Other studies have also suggested that the MSNQ is influenced by psychosocial variables, such as anxiety, rather than by objective status.[13,29,30] The impact of psychosocial variables could be the explanation for the subpopulation of patients who reported high impact on self-experienced cognitive impairment but had normal results on standard neuropsychological testing.

An opposite subgroup with low MSNQ-I and MSNQ-P scores had severe cognitive impairment when tested with formal neuropsychological tests. This might be explained by a coping strategy of the patients and informants to undervalue cognitive impairment and, therefore, report low MSNQ-P and MSNQ-I scores in self-perceived cognitive impairment. Another explanation for low MSNQ-P scores and high cognitive impairment could also be that severely affected patients do not perceive the dementia. Further studies are needed to clarify these issues of self-assessed measures of cognition.

In conclusion, this study does not support use of the MSNQ-P or the MSNQ-I as a sensitive or valid screen-

did find very high sensitivity compared with neuropsychological testing.

Sonder et al[27] demonstrated lower loadings regarding how individual questions are weighted and affect the MSNQ score. Different study populations and cultural differences regarding the content of the questions should also be considered in future studies. Unfortunately, this study was not designed to test for such differences.

Finally, it should be considered whether the MSNQ actually does measure cognitive impairment. Strober et al[28] recently reported that self-assessed measures of cognition do not correlate with systematic neuropsychological testing but rather with quality of life and behavioral

***Table 2.* Correlations between MSNQ-P, MSNQ-I, and SDMT and individual neuropsychological tests**

	Neuropsychological tests				
Measure	**D-S/SS**	**RAVLT**	**TMT-B**	**WCST**	**BNT**
MSNQ-P					
R^2	0.000385	0.00713	0.01447	0.010923	0.002
P value	<.8663	<.4651	<.2974	<.3689	<.6993
MSNQ-I					
R^2	0.058501	0.02064	0.00327	2.158e-6	0.00085
P value	<.0604	<.2652	<.6588	<.9910	<.8217
SDMT					
R^2	0.6736	0.2753	0.4478	0.1272	0.0136
P value	<.0001	<.0001	<.0001	<.0016	<.3113

Note: n = 77. Altogether, no correlations were found between MSNQ-P and MSNQ-I and neuropsychological tests. SDMT correlated with D-S/SS, TMT-B, RAVLT, and WCST.
Abbreviations: BNT, Boston Naming Test; D-S/SS, Digit-Symbol Coding; MSNQ-P and MSNQ-I, Multiple Sclerosis Neuropsychological Screening Questionnaire–Patient and –Informant, respectively; RAVLT, Rey Auditory Verbal Learning Test; SDMT, Symbol Digit Modalities Test; TMT-B, Trail Making Test B; WCST, Wisconsin Card Sorting Test.

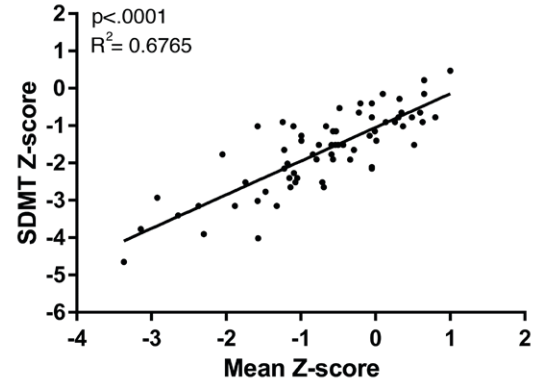

***Figure 4.* Linear fit regression of Symbol Digit Modalities Test (SDMT) and neuropsychological test battery**

Linear fit regression between SDMT scores and mean *z* scores of the neuropsychological tests for individual patients in standard deviations. We found a significant correlation with *z* scores and SDMT scores (R^2 = 0.68, *P* < .0001) (n = 68).

ing tool for cognitive impairment in Danish patients with MS. In contrast, this study found the SDMT to be more reliable owing to higher sensitivity and specificity. Further studies are needed to assess the effect of differences in study populations, choice of cutoff values, and cultural and psychosocial impact. □

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References

1. Glanz BI, Healy BC, Rintell DJ, Jaffin SK, Bakshi R, Weiner HL. The association between cognitive impairment and quality of life in patients with early multiple sclerosis. *J Neurol Sci*. 2010;290:75-79.
2. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis, I: frequency, patterns, and prediction. *Neurology*. 1991;41:685-691.
3. Baumstarck-Barrau K, Simeoni MC, Reuter F, et al. Cognitive function and quality of life in multiple sclerosis patients: a cross-sectional study. *BMC Neurol*. 2011;11:17.
4. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis, II: impact on employment and social functioning. *Neurology*. 1991;41:692-696.
5. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol*. 2010;9:438-446.
6. Hellwig K, Gold R. Progressive multifocal leukoencephalopathy and natalizumab. *J Neurol*. 2011;258:1920-1928.

PRACTICE POINTS

- We studied the validity and reliability of the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ), a screening tool for cognitive impairment, in 126 Danish patients and their informants.
- Test-retest reliability of the MSNQ-Patient (MSNQ-P) was assessed on a subsample of 44 patients and was found to be high. There was a high correlation between the MSNQ-P and the MSNQ-Informant (MSNQ-I).
- The Danish versions of the MSNQ-P and the MSNQ-I showed no correlation with formal neuropsychological testing. In contrast, they demonstrated significant (albeit low) correlation with depression, suggesting correlation of the Danish MSNQ-P and MSNQ-I with behavioral outcomes rather than with neuropsychological measures.

7. Vollmer T, Huynh L, Kelley C, et al. Relationship between brain volume loss and cognitive outcomes among patients with multiple sclerosis: a systematic literature review. *Neurol Sci*. 2016;37:165-179.
8. McCaffrey RJ, Krahula MM, Heimberg RG, Keller KE, Purcell MJ. A comparison of the trail making test, symbol digit modalities test, and the Hooper Visual Organization Test in an inpatient substance abuse population. *Arch Clin Neuropsychol*. 1988;3:181-187.
9. Benedict RH, Fischer JS, Archibald CJ, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. *Clin Neuropsychol*. 2002;16:381-397.
10. Benedict RH, Munschauer F, Linn R, et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Mult Scler*. 2003;9:95-101.
11. Benedict RH, Weinstock-Guttman B, Fishman I, Sharma J, Tjoa CW, Bakshi R. Prediction of neuropsychological impairment in multiple sclerosis: comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Arch Neurol*. 2004;61:226-230.
12. Benedict RH, Zivadinov R. Reliability and validity of neuropsychological screening and assessment strategies in MS. *J Neurol*. 2007;254(suppl 2):II22-II25.
13. O'Brien A, Gaudino-Goering E, Shawaryn M, Komaroff E, Moore NB, DeLuca J. Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes. *Arch Clin Neuropsychol*. 2007;22:933-948.
14. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol*. 2001;50:121-127.
15. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. 1996;67:588-597.
16. Ravnborg M, Blinkenberg M, Sellebjerg F, Ballegaard M, Larsen SH, Sorensen PS. Responsiveness of the Multiple Sclerosis Impairment Scale in comparison with the Expanded Disability Status Scale. *Mult Scler*. 2005;11:81-84.
17. Ravnborg M, Gronbech-Jensen M, Jonsson A. The MS Impairment Scale: a pragmatic approach to the assessment of impairment in patients with multiple sclerosis. *Mult Scler*. 1997;3:31-42.
18. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444-1452.
19. Smith A. *Symbol Digit Modalities Test: Manual*. Los Angeles, CA: Western Psychological Services; 1982.
20. Watson CG, Gasser B, Schaefer A, Buranen C, Wold J. Separation of brain-damaged from psychiatric patients with ability and personality measures. *J Clin Psychol*. 1981;37:347-353.
21. Benedict RH, Cox D, Thompson LL, Foley F, Weinstock-Guttman B, Munschauer F. Reliable screening for neuropsychological impairment in multiple sclerosis. *Mult Scler*. 2004;10:675-678.
22. Vanotti S, Benedict RH, Acion L, Caceres F. Validation of the Multiple Sclerosis Neuropsychological Screening Questionnaire in Argentina. *Mult Scler*. 2009;15:244-250.
23. Benedict RH, Duquin JA, Jurgensen S, et al. Repeated assessment of neuropsychological deficits in multiple sclerosis using the Symbol Digit Modalities Test and the MS Neuropsychological Screening Questionnaire. *Mult Scler*. 2008;14:940-946.
24. Morrow SA, O'Connor PW, Polman CH, et al. Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. *Mult Scler*. 2010;16:1385-1392.
25. Sonder JM, Burggraaff J, Knol DL, Polman CH, Uitdehaag BM. Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. *Mult Scler*. 2014;20:481-488.
26. Van Schependom J, D'Hooghe MB, Cleynhens K, et al. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. *Eur J Neurol*. 2014;21:1219-1225.
27. Sonder JM, Mokkink LB, van der Linden FA, Polman CH, Uitdehaag BM. Validation and interpretation of the Dutch version of the Multiple Sclerosis Neuropsychological Screening Questionnaire. *J Neurol Sci*. 2012;320:91-96.
28. Strober LB, Binder A, Nikelshpur OM, Chiaravalloti N, DeLuca J. The Perceived Deficits Questionnaire: perception, deficit, or distress? *Int J MS Care*. 2016;18:183-190.
29. Akbar N, Honarmand K, Feinstein A. Self-assessment of cognition in multiple sclerosis: the role of personality and anxiety. *Cogn Behav Neurol*. 2011;24:115-121.
30. Langdon DW, Benedict RH, Wicklein EM, Beckmann K, Fredrikson S. Reports of patients and relatives from the CogniCIS study about cognition in clinically isolated syndrome: what are our patients telling us? *Eur Neurol*. 2013;69:346-351.

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Practice effect in Symbol Digit Modalities Test in multiple sclerosis patients treated with natalizumab

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ABSTRACT

Objectives: How practice effect influences cognitive testing measured by monthly Symbol Digit Modalities Test (SDMT) during natalizumab treatment, and what factors confound such effect.
Methods: Eighty patients were examined monthly with SDMT for 26.2 ± 8.4 months. After 26.0 ± 8.1 months, SDMT was also performed with a rearranged key in 59 cases. Results of SDMTs with the rearranged and previous regular key were compared. We examined if gender, age, Extended Disability Status Scale (EDSS), relapses, and disability progression/improvement influence SDMT performed with the regular and the rearranged key, respectively. We also explored if natalizumab applied before regular monthly SDMT may influence practice effect and cognition.
Results: SDMT performance improved by 1.2 points/test during the first six months and by 0.4 points/test thereafter. Rearranging the symbols of the key after 26.0 ± 8.1 months returned SDMT scores to baseline indicating a practice effect. Such practice effect was more significant after longer testing period, but was not influenced by gender, age, relapses, disability progression and prior natalizumab treatment. Although the change from baseline to 2.5 years was significant in subgroups with EDSS 0–3, 3.5–5.5 and 6–7.5, this was higher in patients with EDSS 0–3 compared to 6–7.5.
Conclusions: Practice effect significantly contributes to continuous improvement in SDMT performance during natalizumab treatment: to test cognition, a change in key is required. Practice effect is less pronounced in patients with advanced disease. Cognition remains stable even in patients with progressive disease during more than 2 years of natalizumab treatment indicated by scores corresponding to baseline after changing the key.

1. Introduction

The estimated prevalence of cognitive impairment in MS ranges between 43–70% (Benedict et al., 2006; Rao et al., 1991) both in the early and late stages of the disease. The effect of cognitive impairment on everyday life activities, employment status, and social relationships is prominent (Amato et al., 1995; Banati et al., 2010). Cognitive impairment can occur irrespective of disease duration even in the earliest stages of the disease (Achiron and Barak, 2003; Banati et al., 2010; Glanz et al., 2007) i.e. clinically isolated syndrome (CIS)(Achiron and Barak, 2003; Feuillet et al., 2007; Glanz et al., 2007). Cognitive deficits may develop independently from physical disability and in patients with benign MS (Feuillet et al., 2007; Glanz et al., 2007; Portaccio et al., 2009). Nevertheless, cognitive disturbances have also been shown to correlate with high EDSS scores, and the presence of cognitive decline may predict a more progressive disease course (Banati et al., 2010; Portaccio et al., 2009; Zipoli et al., 2010).

Intellectual disability of MS affects various aspects of general cognitive functioning, including efficiency of information processing, verbal and visuo-spatial memory, executive functioning, attention, and visual perceptual processing. all of which are detectable with sensitive neuropsychological test batteries specially developed for the MS population (Benedict et al., 2006; Rao, 1991). Particularly processing speed and visual memory seem to be most commonly affected (Benedict et al., 2006; Rao et al., 1991).

The Symbol Digit Modalities Test (SDMT) measures processing speed and working memory. This test is recommended in the Brief International Cognitive Assessment for MS (BICAMS) as the cognitive test of choice, when only 5 min of testing is available. SDMT is easy to administer, it does not require trained personnel (Benedict et al., 2008; Langdon et al., 2012), and is an effective tool to detect cognitive decline in clinical practice (Van Schependom et al., 2014).

The effect of natalizumab treatment on cognition has been evaluated by SDMT in a few MS cohorts: these indicated improved

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cognition (Holmen et al., 2011; Iaffaldano et al., 2012; Kunkel et al., 2015; Morrow et al., 2010; Portaccio et al., 2013). The frequency of SDMT testing and follow-up varies in these studies: monthly, 6-monthly, and annual examinations have been applied for 48 weeks up to 2 years (Holmen et al., 2011; Iaffaldano et al., 2012; Kunkel et al., 2015; Morrow et al., 2010; Portaccio et al., 2013). Since one of the earliest symptoms of progressive multifocal leukoencephalopathy (PML) associated with natalizumab treatment is subacute cognitive decline, SDMT can also be an efficient and rapid screening test for subclinical PML in patients infected with JC-virus (Sorensen et al., 2012) before monthly natalizumab infusions. However, potential practice effect may complicate interpretation of SDMT results, i.e. patients using the same SDMT every month become familiar with the test and gain practice.

In this study, therefore we examined cognitive performance with monthly SDMT during natalizumab treatment up to 35 months. We evaluated a possible practice effect by a single change in the order of symbols in SDMT after 26.0 ± 8.1 weeks. We also examined the effect of confounding factors, such as age, gender, disability progression, functional status and natalizumab treatment prior regular introduction of SDMT.

2. Materials and methods

2.1. Study population and design

Eighty patients were enrolled, who have been treated with natalizumab at the Department of Neurology, Odense University Hospital, Denmark (Table 1). The study duration ranged from the implementation of SDMT in November 2011 to September 2014.

Regular SDMT were performed as part of the routine protocol for natalizumab treatment in the region of Southern Denmark. Data were retrospectively reviewed: 2356 individual SDMTs were performed in the study period. The number of consecutive tests per patient varied from 5 to 39, which corresponded to follow up from 4 to 35 months (26.2 ± 8.4 months). Sixty patients (75%) completed 25 consecutive SDMTs, indicating their participation in the study for at least two years. Demographics are summarized in Table 1.

The study was approved by the Regional Scientific Committees for Southern Denmark and the Danish Data Protection Agency.

2.2. Data collection

SDMT was performed every 4th week before natalizumab infusion. Every test was done in 90 s. Trained nurses collected SDMT data. EDSS scores were determined every six months. For all patients, who had been already treated with natalizumab at the implementation of the SDMT in November 2011, baseline EDSS was the latest performed EDSS, which due to routine EDSS scoring, could at maximum be 6-months old. In September 2014, all clinical and SDMT data were retrieved from the hospital database and from the Danish Multiple Sclerosis Database. Data were stratified according to EDSS, gender, age, relapses and natalizumab treatment before the introduction of SDMT testing. Only the first 30 consecutive SDMTs were included for further analyses. Three cohorts were established based on baseline EDSS: ≤3, 3.5-5.5 and ≥6. Three equally sized groups were defined based on the age of the patients. Disability progression was defined as ≥1 point increase of EDSS persisting for at least 6 months retrospectively analyzed at 2 years; improvement was defined as ≥1 point EDSS decrease after 2 years; stable disease was defined if EDSS change was & $2lt;1 point after 2 years.

Table 1
Study design and demographics.

Study design	
Patients treated with natalizumab	80
Male gender	23 (29%)
Female gender	57 (71%)
Patients suffering a relapse during the study	32 (40%)
Patients treated with natalizumab before the study	50 (63%)
Number of natalizumab infusions before the study	38.4 ± 16.4
Mean number of SDMTs per patient	26 ± 7[a]
Mean age at first SDMT (years)	41.0 ± 9.7
Mean baseline EDSS	3.3 ± 2.0
Mean EDSS change during follow up	0.12

Mean ± standard deviation is shown where applicable.
[a] Equals 104 ± 28 weeks follow up.

2.3. Introduction of a new SDMT key

Nine symbols are paired with numbers in the SDMT test (key). A definite sequence of symbols should be paired with the correct number during a timed (90 s) examination. At the end of the study period in September 2014, all patients still treated with natalizumab (59 patients) were examined with two SDMT, approximately one hour apart with the same nine symbols, but the pairing of symbols and numbers in the key was rearranged. The main sequence of 110 symbols in the test remained the same. At that time point, the number of SDMT testing in this cohort ranged from 8 to 38, with a mean number of SDMT 29.3 ± 8.8.

2.4. Statistical analysis

Statistical analyses were performed using STATA/IC version 13.1 for Windows. The Shapiro-Wilks test for normality was used to ensure legitimate use of parametric statistics. To determine an overall pattern in the improvement of SDMT scores, the mean of every consecutive test was plotted, and analyzed using linear regression.

3. Results

3.1. Long-term SDMT performance during natalizumab treatment

To evaluate the long-term SDMT performance, we compared the mean score for each consecutive monthly SDMT. This revealed a clear overall improvement, with an increase in mean raw score up to 30 months. This improvement was most rapid during the first six months, indicated by an approximate improvement of 1.2 point per SDMT. Thereafter, a mean improvement of 0.4 point per SDMT was detected (Fig. 1).

3.2. Examination of practice effect by the introduction of a new key

The SDMT scores improved significantly even after the 4th consecutive monthly test (p=0.009, n=80) and thereafter (Fig. 1). Since a practice effect due to the frequent SDMT can be responsible for such an early and continuous improvement, we investigated the effect of a rearranged key. In September 2014, 59 patients were examined with a novel key in the SDMT: the symbols were the same as baseline but the order was changed within the key. At that time point, 23 patients were followed for more than 34 months, 22 patients were followed for more than two years, and 14 patients were followed for less than 2 years but for at least 8 months (Fig. 2). Changing the key returned the scores to baseline in all groups. This indicated that a practice effect significantly contributed to the improved SDMT performance. Longer testing with frequent SDMT resulted in a more significant improvement (Fig. 2**B**). EDSS had no effect on this pattern, except in patients with EDSS≥6, where changes with the new key were not significant (Fig. 3).

We next investigated the effect of several factors on performance with monthly SDMT over 2 years, i.e. their influence on the practice effect and cognition.

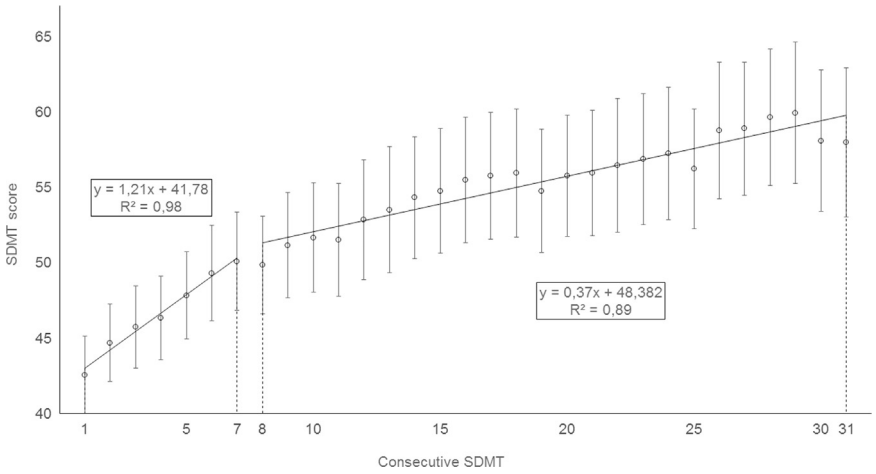

Fig. 1. Change in SDMT performance during 30 months of natalizumab treatment. SDMT was performed monthly during natalizumab treatment of 80 patients with MS. Mean of monthly SDMT scores and 95% confidence intervals are shown up to 31 consecutive SDMTS, i.e. 30 months.

3.3. The effect of disease severity, disability progression and improvement

To investigate relationship between disease severity, cognition, and practice effect, we stratified patients according to EDSS and created three cohorts: EDSS 0–3, 3.5–5.5, and 6–7.5. Monthly SDMT performance and effect of changing the key were examined in these cohorts. Significant increase over 2 years in SDMT scores was detected in the groups with the EDSS≤3 (p & $2lt;0.001) and EDSS 3.5-5.5 (p=0.001). SDMT scores returned to baseline in these subgroups by using the rearranged SDMT key (Fig. 3). In the group with EDSS 6–7.5, baseline SDMT scores were significantly lower (p & $2lt;0.001 versus EDSS 0–3, and p=0.005 versus EDSS 3.5–5.5, respectively). In addition, the change from baseline to 2-year SDMT was not significant in this group (Fig. 3**B**), but became significant after 2.5 years (p=0.03). Nevertheless, the net change of SDMT scores from baseline to 2.5 years was significantly higher in patients with EDSS 0–3 compared to patients with EDSS 6–7.5 (22.68 ± 11.11 and 10.06 ± 5.97, p & $2lt;0.001). Scores returned to baseline after changing the key even in the cohort of EDSS 6–7.5 (Fig. 3**A**).

To examine the effect of disability progression or improvement on SDMT performance and learning ability, patients were also stratified according to disability progression (≥1 point increase of EDSS in 2 years, n=19), improvement (≥1 point EDSS decrease in 2 years, n=14) or stable disease (change less than 1 EDSS point, n=46). A significant increase in SDMT scores during 2 years was observed in all three cohorts (p=0.001, p=0.02 and p & $2lt;0.01 for stable, increased and decreased EDSS, respectively). In addition, SDMT scores returned to baseline in all three cohorts by using the rearranged SDMT key (data not shown).

We also dichotomized the cohort based on a cut-off value below and above 50 of the baseline SDMT, and examined the change of SDMT in the two populations over two years. The mean change of SDMT in patients with baseline SDMT 49 and below was 13.9, while in patients with baseline SDMT 50 and over was 13.4 and this difference was not significant.

3.4. The effect of age, relapse and gender

To investigate if age and disease activity influence cognitive performance and practice effect, we defined three equally sized groups based on age. There was no difference between the youngest and oldest groups comparing SDMT scores at baseline and after 2 years (Fig. 4**A**). The rate of increase in SDMT was also the same in the two groups

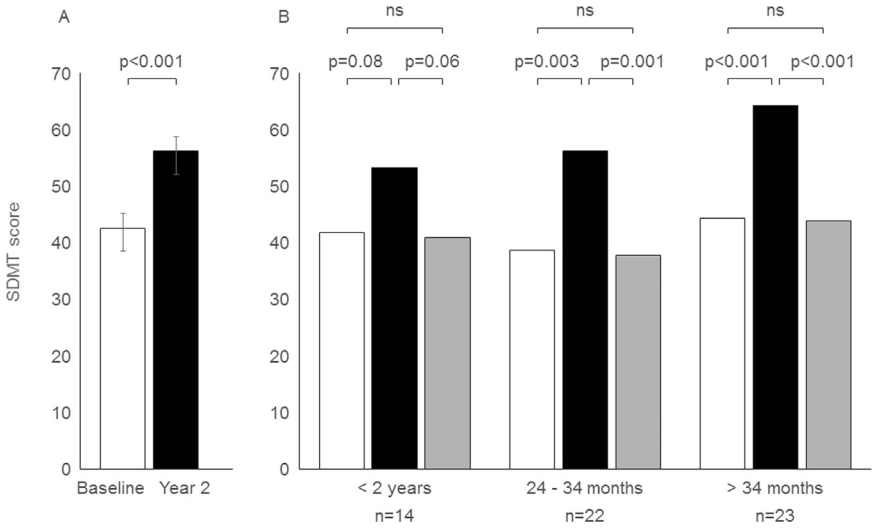

Fig. 2. Practice effect on SDMT performance. A. Mean of monthly SDMT scores are shown before introduction of regular monthly SDMT (baseline, white bar), and 2 years after monthly SDMT (black bar). B. A new key was introduced by rearranging symbols. Patients were grouped according to the length of period with monthly SDMT at the time, when the new key was introduced. White bars indicate baseline values, black bars indicate the latest performed SDMT, and grey bars show SDMT scores obtained with the new key. All bars indicate mean.

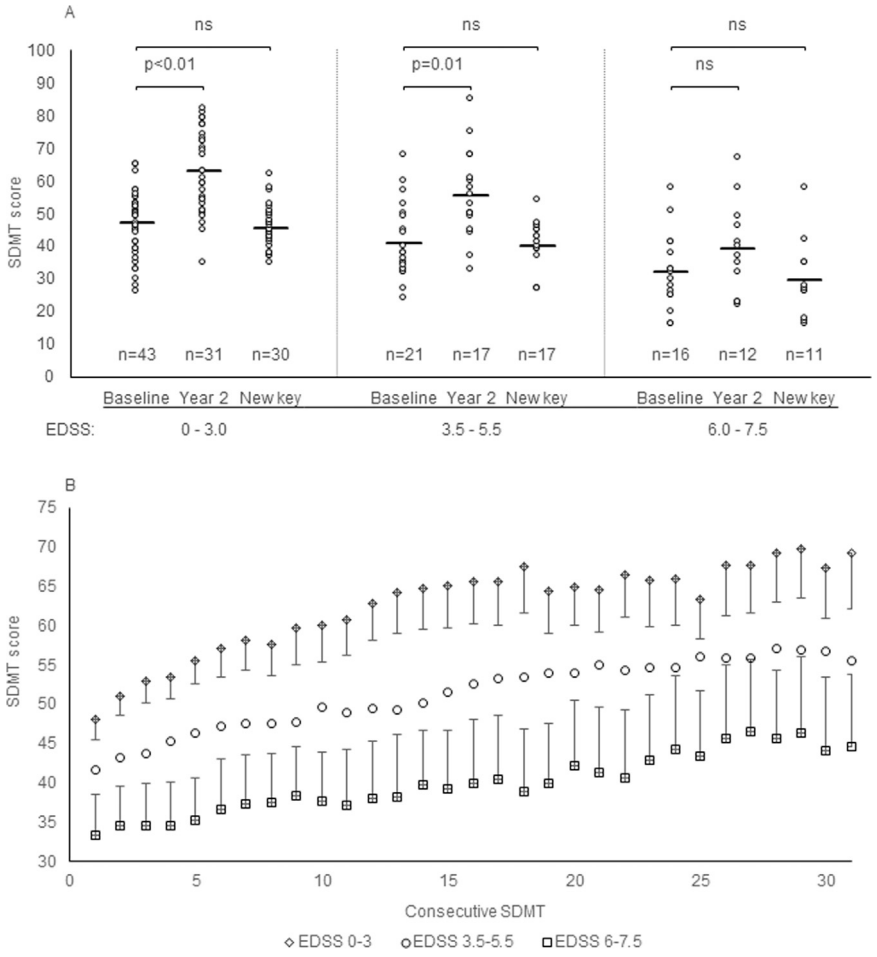

Fig. 3. Effect of EDSS on SDMT scores. A. Patients were stratified into three groups based on EDSS: 0–3.0 (left panel), 3.5–5.5 (middle panel), and 6.0–7.5 (right panel). SDMT scores and mean are shown in the three cohorts: before introduction of regular monthly SDMT (Baseline) to examine effect of functional status on cognitive domains, 2 years after monthly SDMT (Year 2) and after the introduction of a new key with rearranged symbols (New key) to examine the influence on practice effect. B. Mean of monthly SDMT scores and 95% confidence intervals are shown up to 31 consecutive SDMTS, i.e. 30 months within the subgroups of patients with EDSS: 0–3.0, 3.5–5.5 and 6.0–7.5.

(Fig. 4**B**), and changing the key returned scores to baseline in both groups (Fig. 4**A**).

Thirty-two patients (40%) experienced relapse during the study period. This was not reflected in their SDMT results: no difference at either baseline or after 2 years was observed comparing patients suffering from at least one relapse and patients who did not have relapses (Fig. 5**A**). Improved SDMT performance was detected in both groups after 2 years, (p & $2lt;0.01, respectively) (Fig. 5**A**). Changing the key returned scores to baseline in both groups (Fig. 5**A**).

Gender had no effect on SDMT performance, and changing the key similarly returned SDMT scores to baseline in male and female patients (data not shown).

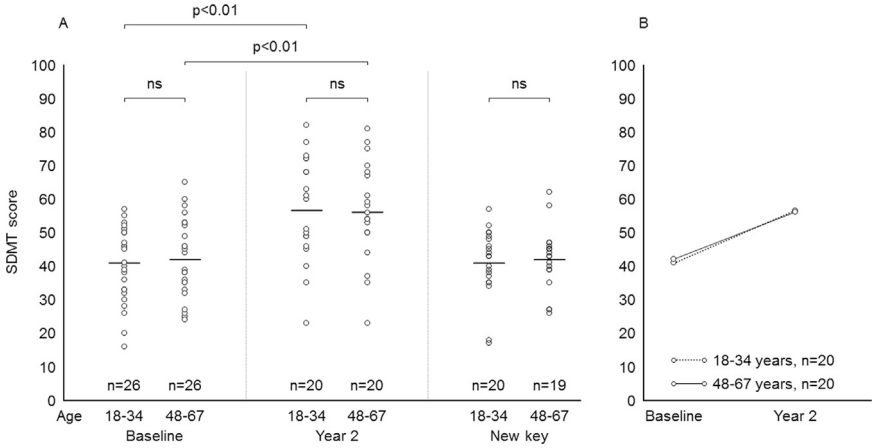

Fig. 4. Effect of age on SDMT scores. SDMT scores before introduction of regular monthly SDMT (Baseline) and 2 years after monthly SDMT (Year 2) are shown in the youngest and oldest one-thirds of the cohort. A. SDMT scores in the youngest and oldest cohorts at baseline, year 2 and with the new key. B. Slope of increase in SDMT scores during 2 years are shown in the youngest and oldest one-thirds of the cohort.

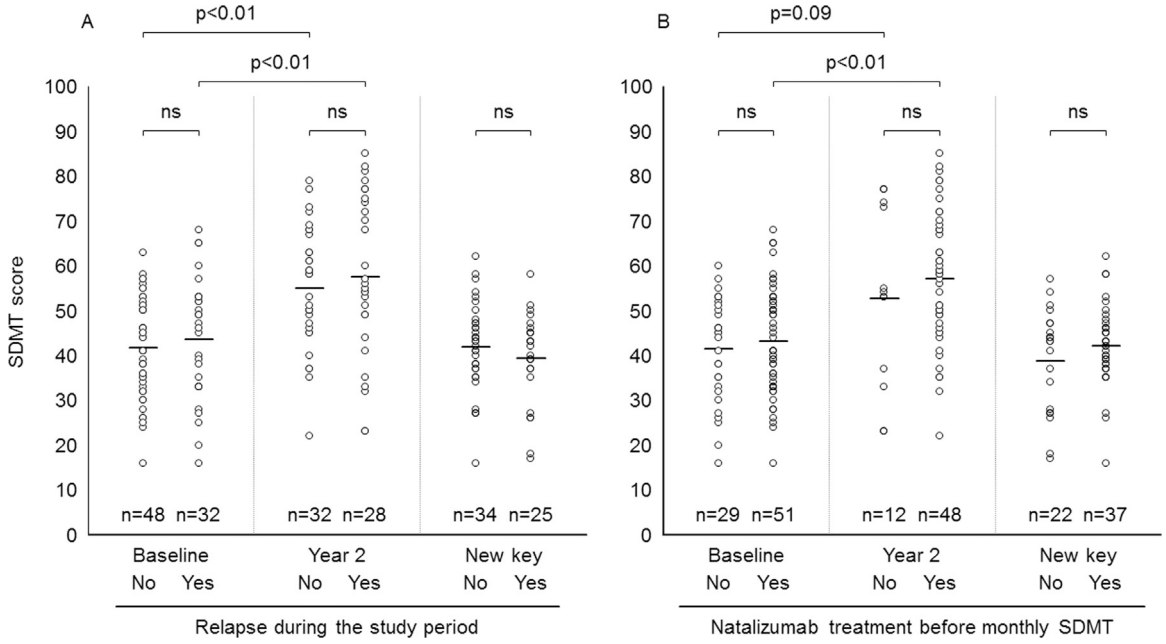

Fig. 5. Effect of relapses and previous natalizumab treatment on SDMT scores. SDMT scores before introduction of regular monthly SDMT (Baseline), 2 years after monthly SDMT (Year 2) and with the new key are shown. A. SDMT scores in the cohorts of patients who did or did not suffer from relapses. B. SDMT scores in a cohort of patients treated with natalizumab before monthly introduction of SDMT (mean duration of treatment 21.9 ± 20.2 weeks) and in a cohort of patients, who simultaneously started natalizumab and regular SDMT testing.

3.5. The effect of natalizumab treatment prior to regular SDMT testing

We also considered that continuous increase in SDMT may also reflect the effect of natalizumab on cognition or even the practice effect. Therefore, we examined the effect of prior natalizumab treatment on the SDMT performance with the regular and the rearranged key. Patients were stratified into two groups: natalizumab before monthly SDMT, i.e. treatment before November 2011 and natalizumab started together with regular SDMT. After 1 and 1.5 year of SDMT testing, there was a significant increase in SDMT in both groups, respectively (year 1: pretreated p & $2lt;0.01 n=51, simultaneously treated p=0.03, n=20; year 1.5: pretreated p & $2lt;0.01, n=50, simultaneously treated p=0.05, n=17)(**Figure 6**). At 2 years, the change in SDMT remained significant in patients pretreated with natalizumab (p & $2lt;0.01 n=48), but was not significant in simultaneously treated patients (p=0.09, n=12) (Fig. 5**B**). Changing the key returned SDMT scores to baseline in both groups (Fig. 5**B**).

4. Discussion

In this study, we examined long-term changes in monthly SDMT performance during natalizumab treatment. We observed a continuous rise in scores up to 30 monthly SDMT over 2.5 years. The increase was most apparent in the first six months of SDMT testing, but mean scores continued to increase by about 0.4 point per test thereafter. Similar continuous increase was also observed in a study with shorter follow up (48 weeks) of monthly testing, and the steepness of the slope also declined over time (Morrow et al., 2010). Testing at every 6 months or annual examination in other studies also resulted in significant improvement after 2 years (Holmen et al., 2011; Iaffaldano et al., 2012).

We considered that such a change in the rate of increase could be due to two reasons. First, it may be caused by a practice effect, i.e. patients using the same SDMT every month become familiar with the test and gain practice. Second, the possible effect of natalizumab treatment on cognition may reach a plateau and only minor improvements can be seen thereafter. Therefore, (i) we explored the effect of a new key on SDMT performance; (ii) we examined confounding factors related to the disease, and (iii) we addressed the effect of natalizumab administered prior to the introduction of regular, monthly SDMT. A previous paper examined the effect of alternate versions of SDMT with different keys in healthy subjects (Benedict et al., 2012). In contrast, here we performed a longitudinal study in MS patients, and (i) examined the evolution of the learning effect over two years, (ii) verified the learning effect by changing the key after two years, and (iii) related the evolution of the learning effect to demographic and clinical characteristics.

We found that a simple change in the order of the symbols completely reversed the increase in SDMT scores and returned it to baseline values, indicating that practice effect significantly impact SDMT results during natalizumab treatment if frequent testing is applied. Longer testing period resulted in better improvement in SDMT performance, which also supports the contribution of practice effect. Such practice effect may be caused by memorization of test stimuli or familiarity with the process itself. However, a single change after more than 2-year frequent testing should not completely abrogate the effect, if only familiarity plays a role. Patients may also have difficulty to adapt to a new key after repetitive usage of the same SDMT version, and this might influence the outcome with the new key. However, it is unlikely that this would be responsible for such dramatic changes in every case. Indeed by using 5 alternate forms of the SDMT, a previous study did not find noticeable differences (Benedict et al., 2012).

Next, we examined confounding factors, which could influence cognition and the observed practice effect during natalizumab treatment. Disability measured by EDSS influenced SDMT results. First, baseline SDMT scores were significantly lower in patients with EDSS≥6 compared to cohorts with lower EDSS. This is consistent with earlier findings that higher EDSS scores correlate with worse performance in different neuropsychiatric tests (Amato et al., 1995). Although SDMT scores were significantly higher after 2.5 years in this subgroup, still the net increase in SDMT scores was significantly lower compared to patients with EDSS 0–3, indicating less practice effect. This could be related to continuous cognitive decline per se and/or to a decreased ability to gain practice during SDMT. It is possible that patients with

advanced disease are no longer able to increase their processing speed as much as less affected patients. Both grey matter and white matter pathology may contribute to such effects as the disease progresses: cortical lesion number, volume and white matter lesion volume independently predicted the performance of information processing speed and working memory, which is measured by SDMT (Mike et al., 2011; Mike and Illes, 2013). Cortical lesion number also predicted verbal learning and memory (Mike et al., 2011; Mike and Illes, 2013; Roosendaal et al., 2009); grey matter pathology becomes prominent with advanced disease and higher EDSS (Kutzelnigg et al., 2005; Lassmann, 2007). Cognitive decline predict a more progressive disease course and seem to be more severe in patients with chronic progressive disease compared to those in the relapsing-remitting stage (Patti et al., 2009; Portaccio et al., 2009; Zipoli et al., 2010). Patients with disability progression, stable disease or improvement also had a significant increase in SDMT scores. But all these cohorts acquired practice effect, indicated by reversal of scores to baseline when using the rearranged key. These data altogether may suggest that patients with higher EDSS may have a deficiency in processing speed, working memory and ability to acquire practice reflected by less increase in SDMT scores after 2.5 years. Nevertheless, there is a practice effect in all EDSS groups.

Four out of ten patients suffered from at least one relapse during the study period, which corresponds to the relapse rate found at two years in the natalizumab phase III trial (Polman et al., 2006). We did not observe a decrease in SDMT scores in patients who experienced relapses at the end of the study period. Previous data suggested 2–3 months temporary decrease (Benedict et al., 2014; Morrow et al., 2011).

We observed that longer SDMT testing period resulted in improvement of SDMT scores. However, these patients were also treated longer with natalizumab, which might have an effect on the practice effect itself by improving cognition. To examine the effect of natalizumab treatment on the practice effect and cognition, we compared a cohort with treatment before monthly introduction of SDMT (21.9 ± 20.2 months) to a cohort of patients, who simultaneously started natalizumab and regular SDMT testing. After 1 and 1.5 year, there was a significant increase in SDMT scores in both groups; although the increase was not significant after 2 years in the group simultaneously treated with natalizumab, this can be explained by lack of statistical power due to the decreasing number of patients. Scores reversed to baseline in both cohorts indicating practice effect. Nevertheless, since these scores were not less than baseline values, this indicated that processing speed and working memory did not decline during this period even in patients with EDSS$\geq$6 or disability progression. Indeed, the effect of natalizumab on cognition has been shown by other cognitive approaches without practice effect (Iaffaldano et al., 2012; Weinstock-Guttman et al., 2012). Second, the observed continuously improving practice effect during natalizumab treatment may be related to maintained cognitive domains.

In summary, our data indicate that repeated monthly testing with SDMT results in a continuous improvement of SDMT scores up to 35 months during natalizumab treatment, which is less pronounced in patients with more advanced disease. Such improvement in performance is largely attributed to a practice effect. Although SDMT is a convenient screening tool for early signs of PML, if consecutively performed, rearrangement of key could make the results more reliable. Finally, the maintained SDMT scores after 2 years compared to baseline and the continuously improving practice effect up to 38 months could be related to the effect of natalizumab on cognitive domains, but this cannot be formally concluded from this retrospective study due to lack of controls without natalizumab treatment.

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Conflicts of interest

Dr. Zsolt Illes and Dr. Tobias Sejbaek have received research support from Biogen Idec and travel grants and speaking fees from Bayer Healthcare, Biogen Idec, Merck Serono, Sanofi-aventis/Genzyme, Teva Pharmaceuticals, and Novartis. MB. Malte Roar has no conflicts of interest to declare.

References

Achiron, A., Barak, Y., 2003. Cognitive impairment in probable multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 74 (4), 443–446.
Amato, M.P., Ponziani, G., Pracucci, G., Bracco, L., Siracusa, G., Amaducci, L., 1995. Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. Arch. Neurol. 52 (2), 168–172.
Banati, M., Sandor, J., Mike, A., Illes, E., Bors, L., Feldmann, A., Herold, R., Illes, Z., 2010. Social cognition and Theory of Mind in patients with relapsing-remitting multiple sclerosis. Eur. J. Neurol. 17 (3), 426–433.
Benedict, R.H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., Weinstock-Guttman, B., 2006. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J. Int Neuropsychol. Soc. 12 (4), 549–558.
Benedict, R.H., Duquin, J.A., Jurgensen, S., Rudick, R.A., Feitcher, J., Munschauer, F.E., Panzara, M.A., Weinstock-Guttman, B., 2008. Repeated assessment of neuropsychological deficits in multiple sclerosis using the Symbol Digit Modalities Test and the MS Neuropsychological Screening Questionnaire. Mult. Scler. (Houndmills Basingstoke Engl.) 14 (7), 940–946.
Benedict, R.H., Morrow, S., Rodgers, J., Hojnacki, D., Bucello, M.A., Zivadinov, R., Weinstock-Guttman, B., 2014. Characterizing cognitive function during relapse in multiple sclerosis. Mult. Scler. (Houndmills Basingstoke Engl.) 20 (13), 1745–1752.
Benedict, R.H., Smerbeck, A., Parikh, R., Rodgers, J., Cadavid, D., Erlanger, D., 2012. Reliability and equivalence of alternate forms for the Symbol Digit Modalities Test: implications for multiple sclerosis clinical trials. Mult. Scler. (Houndmills Basingstoke Engl.) 18 (9), 1320–1325.
Feuillet, L., Reuter, F., Audoin, B., Malikova, I., Barrau, K., Cherif, A.A., Pelletier, J., 2007. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. Mult. Scler. (Houndmills Basingstoke Engl.) 13 (1), 124–127.
Glanz, B.I., Holland, C.M., Gauthier, S.A., Amunwa, E.L., Liptak, Z., Houtchens, M.K., Sperling, R.A., Khoury, S.J., Guttmann, C.R., Weiner, H.L., 2007. Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. Mult. Scler. (Houndmills Basingstoke Engl.) 13 (8), 1004–1010.
Holmen, C., Piehl, F., Hillert, J., Fogdell-Hahn, A., Lundkvist, M., Karlberg, E., Nilsson, P., Dahle, C., Feltelius, N., Svenningsson, A., Lycke, J., Olsson, T., 2011. A Swedish national post-marketing surveillance study of natalizumab treatment in multiple sclerosis. Mult. Scler. (Houndmills Basingstoke Engl.) 17 (6), 708–719.
Iaffaldano, P., Viterbo, R.G., Paolicelli, D., Lucchese, G., Portaccio, E., Goretti, B., Direnzo, V., D'Onghia, M., Zoccolella, S., Amato, M.P., Trojano, M., 2012. Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis: a prospective, open-label, two years observational study. PloS One 7 (4), e35843.
Kunkel, A., Fischer, M., Faiss, J., Dahne, D., Kohler, W., Faiss, J.H., 2015. Impact of natalizumab treatment on fatigue, mood, and aspects of cognition in relapsing-remitting multiple sclerosis. Front. Neurol. 6, 97.
Kutzelnigg, A., Lucchinetti, C.F., Stadelmann, C., Bruck, W., Rauschka, H., Bergmann, M., Schmidbauer, M., Parisi, J.E., Lassmann, H., 2005. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 128 (Pt 11), 2705–2712.
Langdon, D.W., Amato, M.P., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., Hamalainen, P., Hartung, H.P., Krupp, L., Penner, I.K., Reder, A.T., Benedict, R.H., 2012. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult. Scler. (Houndmills Basingstoke Engl.) 18 (6), 891–898.
Lassmann, H., 2007. New concepts on progressive multiple sclerosis. Curr. Neurol. Neurosci. Rep. 7 (3), 239–244.
Mike, A., Illes Z, G.C., 2013. Impact of Gray Matter Pathology on Cognitive Function in Multiple Sclerosis. Neuroimaging - Clinical applications, (Bright P, pp356-372).
Mike, A., Glanz, B.I., Hildenbrand, P., Meier, D., Bolden, K., Liguori, M., Dell'Oglio, E., Healy, B.C., Bakshi, R., Guttmann, C.R., 2011. Identification and clinical impact of multiple sclerosis cortical lesions as assessed by routine 3T MR imaging. AJNR Am. J. Neuroradiol. 32 (3), 515–521.
Morrow, S.A., Jurgensen, S., Forrestal, F., Munchauer, F.E., Benedict, R.H., 2011. Effects of acute relapses on neuropsychological status in multiple sclerosis patients. J. Neurol. 258 (9), 1603–1608.
Morrow, S.A., O'Connor, P.W., Polman, C.H., Goodman, A.D., Kappos, L., Lublin, F.D., Rudick, R.A., Jurgensen, S., Paes, D., Forrestal, F., Benedict, R.H., 2010. Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. Mult. Scler. J. 16 (11), 1385–1392.
Patti, F., Amato, M.P., Trojano, M., Bastianello, S., Tola, M.R., Goretti, B., Caniatti, L., Di Monte, E., Ferrazza, P., Brescia Morra, V., Lo Fermo, S., Picconi, O., Luccichenti, G., Group, C.S., 2009. Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing-remitting multiple sclerosis: baseline results

from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. Mult. Scler. (Houndmills Basingstoke Engl.) 15 (7), 779–788.
Polman, C.H., O'Connor, P.W., Havrdova, E., Hutchinson, M., Kappos, L., Miller, D.H., Phillips, J.T., Lublin, F.D., Giovannoni, G., Wajgt, A., Toal, M., Lynn, F., Panzara, M.A., Sandrock, A.W., Investigators, A., 2006. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N. Engl. J. Med. 354 (9), 899–910.
Portaccio, E., Stromillo, M.L., Goretti, B., Hakiki, B., Giorgio, A., Rossi, F., De Leucio, A., De Stefano, N., Amato, M.P., 2013. Natalizumab may reduce cognitive changes and brain atrophy rate in relapsing-remitting multiple sclerosis–a prospective, non-randomized pilot study. Eur. J. Neurol. 20 (6), 986–990.
Portaccio, E., Stromillo, M.L., Goretti, B., Zipoli, V., Siracusa, G., Battaglini, M., Giorgio, A., Bartolozzi, M.L., Guidi, L., Sorbi, S., Federico, A., Amato, M.P., De Stefano, N., 2009. Neuropsychological and MRI measures predict short-term evolution in benign multiple sclerosis. Neurology 73 (7), 498–503.
Rao, S.M., 1991. A Manual for the Brief Repetable Battery of Neuropsychological Tests in Multiple Sclerosis. New York.
Rao, S.M., Leo, G.J., Bernardin, L., Unverzagt, F., 1991. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 41 (5), 685–691.
Roosendaal, S.D., Moraal, B., Pouwels, P.J., Vrenken, H., Castelijns, J.A., Barkhof, F., Geurts, J.J., 2009. Accumulation of cortical lesions in MS: relation with cognitive impairment. Mult. Scler. (Houndmills Basingstoke Engl.) 15 (6), 708–714.
Sorensen, P.S., Bertolotto, A., Edan, G., Giovannoni, G., Gold, R., Havrdova, E., Kappos, L., Kieseier, B.C., Montalban, X., Olsson, T., 2012. Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. Mult. Scler. (Houndmills Basingstoke Engl.) 18 (2), 143–152.
Van Schependom, J., D'Hooghe, M., Cleynhens, B., D'Hooge, K., Haelewyck, M., De Keyser, M.C., Nagels, G, J., 2014. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. Eur. J. Neurol. 21 (9), 1219–1225, (e1271-1212).
Weinstock-Guttman, B., Galetta, S.L., Giovannoni, G., Havrdova, E., Hutchinson, M., Kappos, L., O'Connor, P.W., Phillips, J.T., Polman, C., Stuart, W.H., Lynn, F., Hotermans, C., 2012. Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS. J. Neurol. 259 (5), 898–905.
Zipoli, V., Goretti, B., Hakiki, B., Siracusa, G., Sorbi, S., Portaccio, E., Amato, M.P., 2010. Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes. Mult. Scler. (Houndmills Basingstoke Engl.) 16 (1), 62–67.

Discussion

Reason for conduct of Thesis

This study focuses on some of the most severe symptoms of MS[1-3] - fatigue and cognitive impairment - and their currently available rating scales. Although there are well-developed rating tools and objective scales for cognition that can be administered by neuropsychologists, physicians, and nurses, regularly applied self-reported tests would offer cost-effective alternative screening methods. In contrast, fatigue can be measured only by self-report. Implementation in trials and daily clinical practice relies on the translation and validation of self-reported questionnaires.

Fatigue

Since outcomes may be biased by cultural and linguistic differences, it is essential that translated PROs are validated in a cohort that represents the native population. We compared our cohort with the original German study cohort used for validation of the FSMC[4], the MFIS as the anchor point.[5] To date, the FMSC has been validated only in German and Danish MS populations.

Whereas the two cohorts were equivalent regarding gender, the Danish cohort was slightly more severely disabled. Its higher EDSS scores could be explained by older age (7.7 years on average) and longer disease duration.

We calculated and found excellent internal consistency, as did Penner et al. in their validation study[4], thus demonstrating the interrelatedness of items and the homogeneity of scale and subscales. The optimal alpha value has, however, been debated, with some statisticians suggesting that high values (> 0.90) may indicate redundancy[6].

Similarly with the previous validation of the FSMC, we found high convergent validity and strong positive correlations among FSMC and MFIS and their subscales.[4] Rather than using the patient-reported MFIS, an objective anchor point of fatigue may have been preferable. However, no studies have succeeded in establishing the connection between fatigue and biomarkers such as inflammatory CSF changes, neurophysiology examination, or structural brain damage measured by MRI.[7] At present, PROs thus offer the best indicators of fatigue.

As expected, both motor subscales showed significant correlations with the EDSS, though only at a weak to moderate level. We found no correlation between FSMC and its cognitive subscales with the BDI-FS score, which supports the use of the FSMC, since many PROs are affected by mood disorders.[8] A sex-based stratification showed that women reported higher levels of fatigue on the FSMC motor subscale ($p < 0.05$) and the MFIS cognitive subscale ($p < 0.05$). As we are not aware of any studies demonstrating higher levels of fatigue in females with MS compared to males, we assume that our findings may be explained by false positives (type I errors) of multiple testing.

The fatigue subscales did not correlate with age, gender or EDSS.

Some of the MFIS test questions revealed differences between the Danish and German cohorts. While this could also reflect a type I error, it may as well suggest a superiority of the FSMC over the MFIS in the Danish MS population, since equal mean scores for the individual FSMC questions were obtained.

When comparing sensitivity and specificity for the different cut-off values for mild (≥ 43), moderate (≥ 53), or severe (≥ 63) fatigue in the Danish and German cohorts, the results were similar, supporting the application of the original German cut-off values in Danish patients. Excellent test accuracy was found for the area under the curve, indicating high reliability in terms of identifying patients with and without fatigue[9, 10]. A bias may lie in lack of a perfect anchor point (MFIS) to distinguish the presence of the symptom.

Our study has some limitations. First, we had no healthy Danish control group. Second, we were unable to check for test-retest reliability. Third, the MFIS has not been validated in Denmark.

In conclusion, besides excellent internal consistency and accuracy, the FSMC has high convergent validity with another measure of fatigue (MFIS). Our results indicate that the FSMC is an applicable and recommendable measure of fatigue in Danish MS patients.

Self-reported cognition

Following the validation of the FSMC, we created a Danish version of the MSNQ and validated it in a Danish MS cohort. We found good test–retest reliability, but no significant correlation with cognitive impairment as measured by five different gold standard neuropsychological tests similar to BICAMS.[11] Our results contrast with positive validation studies published in Argentine Spanish, Dutch, and American English,[12-15] as we were unable to establish correlation between MSNQ results and any of the applied neuropsychological tests. The SDMT seems a better choice for screening for cognitive impairment, as four out of five neuropsychological tests showed good correlation with SDMT again in contrast to the MSNQ that didn't correlated with any of the neuropsychological tests.

We speculate that the study may have been underpowered, since the majority of patients were within the normal range of cognitive performance, as determined by *Z*-scores in the five neuropsychological tests. Another possibility is that the MSNQ questions may be unsuitable for a Danish population. In our fatigue validation study, we found different scores for the Danish and German cohorts on a number of questions. The Dutch validation study of MSNQ[16] also demonstrated differences in the weighting of individual questions and MSNQ scores. Differences in demographics and culture of study cohorts with regard to the interpretation of questions should therefore be considered. In contrast to our fatigue validation study, we were not able to compare the Danish cohort with the original MSNQ validation cohort, because those data are not public. The most recent validation of the MSNQ in another language was published in 2009.[15] A publication bias may be also considered, as negative results in other languages may not have been published.[17, 18]

The low sensitivity and specificity of the MSNQ in our study may have several explanations. While we used the same MSNQ cut-off value of 26 as the original validation study,[19] different cut-off values were applied by other studies to achieve higher sensitivity and specificity; the optimal cut-off point thus seems to change from study to study.[14-16] Tests using other cut-off points failed to increase the sensitivity or specificity in our cohort.

In comparison with previous studies, our cohort had a shorter average disease duration (eight years) and lower disability (2.8 EDSS). This may also explain our relatively low proportion of cognitively impaired patients (13 out of 77) [14-16]. However, a sensitive screening tool for cognitive impairment in younger MS cohorts and in patients with shorter disease duration would be useful. Ideally, longitudinal examinations and repeated testing should be preferable even in patients with normal cognition in order to assess cognitive decline.

Most MS patients have normal intellect before disease onset, which is usually in early adulthood. High brain reserve protects against cognitive impairment in MS.[20] The cross-sectional study design presents a limitation; we thus failed to address the possibility that MSNQ may detect relative change in cognition over time; patients performing above the 50th percentile who lose 1.5 SD would thus not be detected with the current definition, as they remained within the normal range (1.5SD below average) of cognitive impairment. This, however, seems unlikely and would be a problem in all studies with cross-sectional designs.

Finally, it should be considered whether the MSNQ offers a true measure of cognitive impairment. Self-reported cognition measures show poor correlation with systematic neuropsychological testing. One previous study has shown better correlation with quality of life and behavioral data[8] than systematic neuropsychological testing and MSNQ. We thus found that both MSNQ-I and MSNQ-P correlated significantly with BDI scores. Other studies have likewise suggested that MSNQ is influenced by psychosocial variables, such as anxiety[14, 21, 22]. The impact of psychosocial variables could explain the high impact on self-experienced cognitive impairment reported by the subpopulation of the patients who showed normal results on standard neuropsychological testing. Interestingly, another subgroup, with low MSNQ-I and MSNQ-P scores, showed severe cognitive impairment when tested with formal neuropsychological tests. This may reflect the informants' coping strategy resulting in an underestimation of cognitive impairment. An alternative explanation for low MSNQ-P and high cognitive impairment could be that severely affected patients do not perceive dementia. Further studies are needed to clarify these issues raised by self-assessment of cognition.

In contrast to our findings regarding the MSNQ, we found a strong significant correlation between SDMT and neuropsychological test battery scores, which demonstrates the relevance of the former for daily clinical monitoring of cognitive impairment in MS, and shows that the SDMT results are similar to those of other MS cohorts[23-26].

In conclusion, whereas our study does not support the use of the MSNQ-P or MSNQ-I as sufficiently valid or sensitive screening tools for cognitive impairment in Danish MS patients, it does show that the higher sensitivity and specificity of the SDMT makes it a more reliable measure. Further studies are needed to assess the impact of cultural and psychosocial differences in study populations, and the impact of cut-off values in different populations.

Objective measures of cognition

In our examination of long-term changes in SDMT scores during natalizumab treatment, we observed a continuous increase in scores when the test was performed every month for 2.5 years. The highest increases were seen during the first six months of testing, but mean scores continued to increase by about 0.4 point per test. Similar results have been reported in a 48-week study, in which the steepness of the slope also declined over time[24]. Studies using yearly or twice-yearly testing rather than monthly testing, also demonstrated significant improvement after two years[27, 28]. Two explanations are possible for the continuous increase in SDMT scores during natalizumab treatment: First, they may be caused by the practice effect gained by performing the same test every month. Second, the possible effect of treatment on cognition may reach a plateau, after which only minor improvements occur.

We therefore explored the effect of a new key on SDMT performance: we examined confounding factors related to the disease, and addressed the effects of natalizumab administered prior to the introduction of regular monthly SDMT testing. In a previous paper, Benedict et al[29] examined the effects of an alternate version of SDMT in a longitudinal study; we examined the change in monthly SDMT scores, and evaluated the change with an alternate SDMT version.

We found that a simple change in the order of the symbols reversed the increase in SDMT scores to baseline values, indicating a significant practice effect of frequent testing with SDM during natalizumab treatment. Longer testing periods resulted in greater improvements in SDMT performance, which also supports the existence of a practice effect. Memorization of test stimuli or familiarity with the process itself may be involved. However, if only familiarity plays a role, a single change after frequent testing over more than two years should not completely abrogate the effect. Patients may also have difficulty adapting to a new key. However, it is unlikely that this would be responsible for the consistently large changes observed. Indeed, by using five alternate forms of the SDMT, a previous study by Benedicte et al. did not find noticeable differences[29]. A study published subsequent to our paper demonstrated stable SDMT scores over two years of treatment with natalizumab, when using five different SDMT keys[30]. Such improvements in SDMT due to practice effect should be considered in trial designs and in measuring changes in SDMT scores over time. In a study designed with a baseline SDMT, the same SDMT was administered again after 4 weeks, reporting increasing scores for subgroups of MS patients treated with slow-release fampridine. The improvement in scores observed in that study is similar to our results, making it unlikely that the slow-release fampridine improved SDMT scores on a group level[31, 32].

Next, we examined confounding factors that might influence cognition, the practice effect, and explain the changes observed in SDMT during natalizumab treatment. Disability, as measured by EDSS, was found to influence the baseline SDMT and also the practice effect. Baseline SDMT scores were significantly lower in patients with EDSS ≥ 6 compare to patients with lower EDSS scores. This is consistent with earlier findings that higher EDSS scores correlate with poorer performance in a range of neuropsychiatric tests[1]. Although SDMT scores in the more disabled subgroups also showed an increase for 2.5 years, the net increase in scores was significantly smaller in these groups than in patients with EDSS scores between 0 and 3, which indicates a smaller practice effect. This could be related to cognitive worsening or to a decreased ability to profit from practice during SDMT, so that patients with advanced disease are unable to increase their processing speed as much as less affected patients. With progress of the disease, both grey matter and white matter pathology may contribute to such effects. Both the extent and severity of cortical and white matter lesions independently predicted information processing speed and working memory performance, which are measured by SDMT[33]. The number of cortical lesion attacks also predicted verbal learning and memory[33, 34]; grey matter pathology has been found to gain prominence with advanced disease and higher EDSS scores[35, 36]. Cognitive decline predicts a more progressive disease course and seems to be more severe in patients with chronic progressive disease than in those in the relapsing-remitting stage[37-39]. Taken together, the data suggest that patients with higher EDSS scores may have deficiencies in processing speed, working memory, and the ability to acquire practice, reflected by a smaller increase in SDMT scores after 2.5 years. Nevertheless, a practice effect was demonstrated in all EDSS groups.

Four out of ten patients in our study suffered from at least one relapse during the study period, which corresponds to the relapse rate found at two years in the natalizumab phase III trial[40]. We did not observe a decrease in SDMT scores at the end of the study period among patients who experienced relapses during the study, though previous data suggested a temporary decrease lasting 2–3 months[41, 42]. The underreporting of relapse activity may indicate bias, since patients experience milder relapses during natalizumab treatment, leading to a possible underestimation in retrospective studies[43, 44].

To examine the effect of treatment on the practice effect and cognition, we compared a cohort who received natalizumab before the introduction of monthly SDM testing (21.9 ± 20.2 months) to a cohort that started natalizumab and regular SDMT testing simultaneously. After 12 and 18 months, both groups showed significant increases in SDMT scores. Although the second group showed non-significant increases after two years, this can be explained by a lack of statistical power due to the decreasing number of subjects. The practice effect was indicated by the reverting of scores to baseline in both cohorts. Nevertheless, since the scores after re-testing with the new key never declined below baseline values, we conclude that processing speed and working memory did not worsen during the treatment, even in patients with EDSS ≥ 6 or with disability progression. Indeed, the effect of natalizumab on cognition has been shown by other studies but the learning effect has not been considered before[28, 45]. Second, the continuous improvement in the practice effect during natalizumab treatment may also be related to maintained cognitive domains.

In summary, our data indicate that patients in natalizumab treatment will show continuous improvement of SDMT results up to 35 months with repeated monthly testing. The increase is less pronounced in patients with more advanced disease. Such performance improvement is largely attributed to a practice effect. Although SDMT is a convenient screening tool for early signs of PML, if consecutively performed, the rearrangement of keys is likely to offer more reliable results, even though a certain practice effect has been observed even when five different SDMT versions were used.[30] The maintenance of SDMT scores after two years compared to baseline, and the continuously improving practice effect up to 38 months, could be related to the effects of natalizumab on cognitive domains, although the lack of controls without natalizumab treatment prevents us from drawing a formal conclusion from this retrospective study. Finally, the practice effect itself may reflect cognitive capacities; consideration as a cognitive tool may be interesting to test.

References

1. Amato MP, Ponziani G, Pracucci G, et al. Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. *Archives of neurology* 1995; 52: 168-172. 1995/02/01.
2. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2003; 9: 219-227. 2003/06/20. DOI: 10.1191/1352458503ms904oa.
3. Minden SL, Frankel D, Hadden L, et al. The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2006; 12: 24-38. 2006/02/08. DOI: 10.1191/135248506ms1262oa.
4. Penner IK, Raselli C, Stocklin M, et al. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2009; 15: 1509-1517. 2009/12/10. DOI: 10.1177/1352458509348519.
5. Flachenecker P, Kumpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2002; 8: 523-526. 2002/12/12. DOI: 10.1191/1352458502ms839oa.

6. Tavakol M and Dennick R. Making sense of Cronbach's alpha. *Int J Med Educ* 2011; 2: 53-55. DOI: 10.5116/ijme.4dfb.8dfd.
7. Biberacher V, Schmidt P, Selter RC, et al. Fatigue in multiple sclerosis: Associations with clinical, MRI and CSF parameters. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2017: 1352458517712078. 2017/05/26. DOI: 10.1177/1352458517712078.
8. Strober LB, Binder A, Nikelshpur OM, et al. The Perceived Deficits Questionnaire: Perception, Deficit, or Distress? *International journal of MS care* 2016; 18: 183-190. DOI: 10.7224/1537-2073.2015-028.
9. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian journal of internal medicine* 2013; 4: 627-635. 2013/09/07.
10. Swets JA. ROC analysis applied to the evaluation of medical imaging techniques. *Investigative radiology* 1979; 14: 109-121. 1979/03/01.
11. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Multiple sclerosis (Houndmills, Basingstoke, England)* 2012; 18: 891-898. 2011/12/23. DOI: 10.1177/1352458511431076.
12. Benedict RH, Cox D, Thompson LL, et al. Reliable screening for neuropsychological impairment in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2004; 10: 675-678.
13. Benedict RH and Zivadinov R. Reliability and validity of neuropsychological screening and assessment strategies in MS. *Journal of neurology* 2007; 254 Suppl 2: II22-II25.
14. O'Brien A, Gaudino-Goering E, Shawaryn M, et al. Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes. *Arch Clin Neuropsychol* 2007; 22: 933-948.
15. Vanotti S, Benedict RH, Acion L, et al. Validation of the Multiple Sclerosis Neuropsychological Screening Questionnaire in Argentina. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2009; 15: 244-250.
16. Sonder JM, Mokkink LB, van der Linden FA, et al. Validation and interpretation of the Dutch version of the Multiple Sclerosis Neuropsychological Screening Questionnaire. *J Neurol Sci* 2012; 320: 91-96. 2012/07/19. DOI: 10.1016/j.jns.2012.06.024.
17. Chalmers I. Underreporting research is scientific misconduct. *Jama* 1990; 263: 1405-1408. 1990/03/09.
18. Dickersin K. The existence of publication bias and risk factors for its occurrence. *Jama* 1990; 263: 1385-1389. 1990/03/09.
19. Benedict RH, Munschauer F, Linn R, et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2003; 9: 95-101.
20. Sumowski JF, Rocca MA, Leavitt VM, et al. Brain reserve against physical disability progression over 5 years in multiple sclerosis. *Neurology* 2016; 86: 2006-2009. 2016/05/11. DOI: 10.1212/wnl.0000000000002702.
21. Akbar N, Honarmand K and Feinstein A. Self-assessment of cognition in Multiple Sclerosis: the role of personality and anxiety. *Cogn Behav Neurol* 2011; 24: 115-121. 2011/09/10. DOI: 10.1097/WNN.0b013e31822a20ae.

22. Langdon DW, Benedict RH, Wicklein EM, et al. Reports of patients and relatives from the CogniCIS study about cognition in clinically isolated syndrome: what are our patients telling us? *Eur Neurol* 2013; 69: 346-351. 2013/05/03. DOI: 10.1159/000345698.
23. Benedict RH, Duquin JA, Jurgensen S, et al. Repeated assessment of neuropsychological deficits in multiple sclerosis using the Symbol Digit Modalities Test and the MS Neuropsychological Screening Questionnaire. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2008; 14: 940-946.
24. Morrow SA, O'Connor PW, Polman CH, et al. Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2010; 16: 1385-1392. 2010/08/27. DOI: 10.1177/1352458510378021.
25. Sonder JM, Burggraaff J, Knol DL, et al. Comparing long-term results of PASAT and SDMT scores in relation to neuropsychological testing in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)*.
26. Van Schependom J, D'Hooghe M B, Cleynhens K, et al. The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. *European journal of neurology* 2014; 21: 1219-e1272. 2014/05/23. DOI: 10.1111/ene.12463.
27. Holmen C, Piehl F, Hillert J, et al. A Swedish national post-marketing surveillance study of natalizumab treatment in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2011; 17: 708-719. 2011/01/14. DOI: 10.1177/1352458510394701.
28. Iaffaldano P, Viterbo RG, Paolicelli D, et al. Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis: a prospective, open-label, two years observational study. *PloS one* 2012; 7: e35843. 2012/05/05. DOI: 10.1371/journal.pone.0035843.
29. Benedict RH, Smerbeck A, Parikh R, et al. Reliability and equivalence of alternate forms for the Symbol Digit Modalities Test: implications for multiple sclerosis clinical trials. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2012; 18: 1320-1325. 2012/01/27. DOI: 10.1177/1352458511435717.
30. Jacques FH, Harel BT, Schembri AJ, et al. Cognitive evolution in natalizumab-treated multiple sclerosis patients. *Multiple sclerosis journal - experimental, translational and clinical* 2016; 2: 2055217316657116. 2017/06/14. DOI: 10.1177/2055217316657116.
31. Jensen H, Ravnborg M, Mamoei S, et al. Changes in cognition, arm function and lower body function after slow-release Fampridine treatment. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2014; 20: 1872-1880. 2014/05/24. DOI: 10.1177/1352458514533844.
32. Jensen HB, Mamoei S, Ravnborg M, et al. Distribution-based estimates of minimum clinically important difference in cognition, arm function and lower body function after slow release-fampridine treatment of patients with multiple sclerosis. *Multiple sclerosis and related disorders* 2016; 7: 58-60. 2016/05/31. DOI: 10.1016/j.msard.2016.03.007.
33. Mike A, Glanz BI, Hildenbrand P, et al. Identification and clinical impact of multiple sclerosis cortical lesions as assessed by routine 3T MR imaging. *AJNR American journal of neuroradiology* 2011; 32: 515-521. 2011/02/12. DOI: 10.3174/ajnr.A2340.
34. Roosendaal SD, Moraal B, Pouwels PJ, et al. Accumulation of cortical lesions in MS: relation with cognitive impairment. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2009; 15: 708-714. 2009/05/14. DOI: 10.1177/1352458509102907.
35. Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain : a journal of neurology* 2005; 128: 2705-2712. 2005/10/19. DOI: 10.1093/brain/awh641.

36. Lassmann H. New concepts on progressive multiple sclerosis. *Current neurology and neuroscience reports* 2007; 7: 239-244. 2007/05/10.
37. Patti F, Amato MP, Trojano M, et al. Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing-remitting multiple sclerosis: baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2009; 15: 779-788. 2009/06/23. DOI: 10.1177/1352458509105544.
38. Portaccio E, Stromillo ML, Goretti B, et al. Natalizumab may reduce cognitive changes and brain atrophy rate in relapsing-remitting multiple sclerosis--a prospective, non-randomized pilot study. *European journal of neurology* 2013; 20: 986-990. 2012/10/13. DOI: 10.1111/j.1468-1331.2012.03882.x.
39. Zipoli V, Goretti B, Hakiki B, et al. Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2010; 16: 62-67. 2009/12/10. DOI: 10.1177/1352458509350311.
40. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *The New England journal of medicine* 2006; 354: 899-910. 2006/03/03. DOI: 10.1056/NEJMoa044397.
41. Benedict RH, Morrow S, Rodgers J, et al. Characterizing cognitive function during relapse in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2014; 20: 1745-1752. 2014/05/21. DOI: 10.1177/1352458514533229.
42. Morrow SA, Jurgensen S, Forrestal F, et al. Effects of acute relapses on neuropsychological status in multiple sclerosis patients. *Journal of neurology* 2011; 258: 1603-1608. 2011/03/09. DOI: 10.1007/s00415-011-5975-3.
43. Lublin FD, Cutter G, Giovannoni G, et al. Natalizumab reduces relapse clinical severity and improves relapse recovery in MS. *Multiple sclerosis and related disorders* 2014; 3: 705-711. 2015/04/22. DOI: 10.1016/j.msard.2014.08.005.
44. Scott TF, Kieseier BC, Newsome SD, et al. Improvement in relapse recovery with peginterferon beta-1a in patients with multiple sclerosis. *Multiple sclerosis journal - experimental, translational and clinical* 2016; 2: 2055217316676644. 2017/06/14. DOI: 10.1177/2055217316676644.
45. Weinstock-Guttman B, Galetta SL, Giovannoni G, et al. Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS. *Journal of neurology* 2012; 259: 898-905. 2011/10/20. DOI: 10.1007/s00415-011-6275-7.

Practice points based on results

FSMC

- The FSMC is an applicable measure of fatigue in Danish MS patients.
- The Danish FSMC correlated well with the original validation of the scale.
- The FSMC had a high reliability and internal consistency in the Danish cohort.

MSNQ

- Test–retest reliability of the MSNQ patient self-report version was found to be high. There was a high correlation between MSNQ-Patient and MSNQ-Informant.
- The Danish version of MSNQ showed no correlation with neuropsychological testing, which may debate its application in the Danish population.
- The Danish MSNQ demonstrated significant (albeit low) correlation with depression, suggesting a correlation with behavioral outcomes rather than with neuropsychological measures.
- Validation studies in the native language are needed before implementation in clinical situations or in scientific studies in order to avoid false positive results related to cultural and linguistic differences.

SDMT

- Monthly SDMT scores improve continuously in patients with MS, even after two years.
- Using a new key reverts SDMR scores to baseline, indicating a practice effect.
- A change of key is required with repeated application of SDMT.
- The practice effect was unrelated to age, relapses, and previous natalizumab treatment, but was affected by disability.
- Cognition measured by SDMT was stable over two years on natalizumab treatment.